Neuman, Keir 2020 A

Dr. Keir Neuman Oral History 2020 A

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Keir Neuman Oral History by David Zierler

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DAVID ZIERLER: This is David Zierler, oral historian for the American Institute of Physics. It's my great pleasure to be here with Dr. Keir Neuman on March 12th, 2020. And Dr. Neuman, can you give us your job title and your affiliation here at NIH?

KEIR NEUMAN: Yes. So my job title is senior investigator. My affiliation is with the Heart, Lung and Blood Institute at the National Institutes of Health.

ZIERLER: All right. And are you comfortable coming a little closer just for the audio pickup?

NEUMAN: Yeah, absolutely.

ZIERLER: Perfect. OK, so let's start at the beginning. Birthplace, family, childhood—tell me all about it.

NEUMAN: So it was an interesting starting. My dad actually—before I was born, my dad was a draft dodger, and so as a result, my parents are both from California, but I was born in Edmonton, Alberta, Canada, when my father was in graduate school.

ZIERLER: What did the citizenship work out for you? What was that like?

NEUMAN: So the citizenship actually was great because it was—so this was obviously at the tail end of the Vietnam War, 1969, and so at that time, the children of U.S. citizens born abroad could apply for actually dual citizenship. So I'm a dual citizen, so I've taken advantage of that. I'm a Canadian and an American citizen, and that made life much easier for me growing up.

ZIERLER: Have you taken advantage of that, of having the Canadian citizenship?

NEUMAN: I grew up in Canada and then could establish American citizenship when I eventually moved here. But it's always an option to go back. And my children—both my daughters are Canadian citizens.

ZIERLER: Oh, really?

NEUMAN: Yeah.

ZIERLER: OK, by virtue of yours?

NEUMAN: Exactly. Yep, yep, yep.

ZIERLER: Wow.

NEUMAN: So Canada is very generous about that, and the U.S. is OK with sort of dual Canada-U.S. citizenship. So for example during the Gulf War, I was all prepared, right? Had we instituted the draft, I was going to go back to Canada and hide out there.

ZIERLER: Now, you said your father was in graduate school at the time.

NEUMAN: Yeah.

ZIERLER: What was he studying?

NEUMAN: He came in psychology and ended up finishing in pharmacology. So he's actually a neuroscientist. And I think a great deal of my sort of start in physics and science was really growing up in a household with a scientist father.

ZIERLER: So his degree, he finished up in pharmacology?

NEUMAN: In pharmacology, yep. In neuropharmacology. That's right.

ZIERLER: OK. And what was his career? What did he do?

NEUMAN: So from there, he was a postdoc in Montreal for ten months, and then was very keen to get a job and ended up taking a faculty position in Newfoundland, of all places. So at Memorial University of Newfoundland. So I mostly grew up in Newfoundland, that sort of island on the extreme east coast of Canada. And he taught in the med school and was a basic scientist. Did patch clamp methods, which is an interesting tie-in to single molecule biophysics that I ended up doing in funny ways. And ironically he actually as I guess a teenager went to Berkeley on early admission. He got in like a year before he graduated from high school. He was actually—or he finished high school a year early, went to Berkeley, wanted to study physics—and this was in the early '60s—had way too much fun doing other things, and got tossed out!

ZIERLER: [laugh]

NEUMAN: But it's a nice circular story about me coming back eventually studying physics at Berkeley. I like to needle him about that.

ZIERLER: There you go. And your mom?

NEUMAN: My mom really raised my sister and I. She's an interesting—she's actually sort of numerically brighter and has a higher IQ than my father. An autodidact. But really didn't—focused really on the two kids for our whole lives.

ZIERLER: And your sister was born in Canada, also?

NEUMAN: In Canada, yeah. Nine years after I was. So she was born in Newfoundland.

ZIERLER: Are your parents still with us?

NEUMAN: Yeah, still with us.

ZIERLER: In Canada?

NEUMAN: My mom's still in Canada, and my dad now lives in San Diego.

ZIERLER: OK. So with your father in that line of work, you were sort of—it was up close and personal to you from the beginning, essentially.

NEUMAN: Yep, up close and personal. And also, I really look back at this—I was a very curious child. Also, I suffer from dyslexia, so I couldn't read—I didn't read until very late. But I was really fortunate that both my parents read to me extensively. So I grew up in this sort of culture of reading. And my dad was bored of children's books, so by the time I was like five, we were reading—

ZIERLER: [laugh] Stuff that would interest him.

NEUMAN: Right. *The Lord of the Rings*, when I was five. And so I really benefited from that, and that was a very close relationship. Hours and hours and hours spent reading. And then that curiosity and trips and road trips and—all day long, it was the sort of back-of-the-envelope kinds of calculations of things. And it was just so critical for physics. And we would just see something and—"Well, let's think about how many strokes are there that the car is going to take." "And the pistons in the car, how many is that going to have in the lifetime of the car? Let's compare that with how many beats of your heart over your lifetime." And these sort of things—it was just constant. And my questions were always answered, and we'd have these long discussions about various things. So I really grew up in this sort of environment of question and think about things and how do you address things from first principles, essentially, which is very much a physics approach to things. I feel like that was the formation of becoming a scientist, without really knowing it. I was just curious, and having this environment where all my questions were not necessarily answered, but entertained, and it was this process of discussion, and one question leading to the next to the next to the next.

ZIERLER: And your formal education in Newfoundland, was it a strong math and science background there was well?

NEUMAN: No, it was terrible. [laugh]

ZIERLER: Really!

NEUMAN: Yeah. So first of all, I was delayed in school because I couldn't read or write. So actually my reading—I was eight, I think, when I learned how to read, and that was a—I was a special project for a PhD or master's student in the education department that was teaching me how to read, basically. And then the schooling in Newfoundland was terrible. And so I sort of—I think a lot of it, again, I learned at home, and really sort of—that environment at home, where my dad—I had enough physics and math, so he taught me at home, and the school itself was sort of abysmal.

ZIERLER: So how in the world did that prepare you to get to Berkeley?

NEUMAN: Yeah, yeah, so I was very fortunate. So the two things—I ended up—we didn't really have an honor's program, but we had—so Canada is officially bilingual, and so elementary school was in this little tiny backwater. We lived right outside the capital. It was a community of like 5,000 and one little elementary school. But then there was a program called French immersion that was for grades seven on. So that sort of became the equivalent of an honors program, because you had to test in, and you had to have more just interest among the parents, really. And so that became a collection of people who were a little bit more sort of academic insight or academic interests at least. So that helped, being surrounded by people who were very bright and smart. And then because I was in French immersion, my dad ended up doing a sabbatical year in Paris, and that I credit with rescuing me intellectually. Because I had sort of been—school was easy. I stopped going; I still got straight A's. It was just not challenging. And so after grade ten, my dad did a sabbatical year, and by hook and by crook, I got into a public high school in Paris. I effectively repeated what would have been the tenth grade, and I've never worked so hard in my life. And I credit that with sort of rescuing me. I feel like I was sort of diverging away from being intellectually capable in some sense, or having that work ethic.

ZIERLER: Did your dad have an institutional affiliation in Paris, or he was just there to write?

NEUMAN: No, he was there—he had an institutional affiliation with the Hospital Necker. So he had a colleague who had actually recently moved. And he was actually going to go to someplace else in France. And part of the reason for this was because both my sister and I were in French immersion, and so he thought going to France could be a perfect opportunity for us to sort of perfect our French and learn the culture. And it just turned out before we ended up arriving, his colleague moved from another university to this hospital, Necker, right in Paris. We lived right outside of Paris. And I sort of snuck into a high school. It was a complicated story, getting into the high school, but eventually I got into high school, and they just treated me like another student. There was nothing special. In Chinatown was where my high school was.

ZIERLER: And your French was strong enough where you were able to slot right in?

NEUMAN: Well, yes and no. [laugh] So the funny thing was, yeah, as I said, I just—I've never worked so hard in my life.

ZIERLER: Now, not just because of the language barrier; because just the rigor of the academics.

NEUMAN: The rigor of the—yeah. The academic rigor was astonishing. But the comment at the end of the year was that—so I had had four years of French immersion in Canada, and so nominally I spoke French, and the comment at the end of the year from my high school teachers was that I had done pretty well "for someone who couldn't speak French when he got there."

ZIERLER: [laugh]

NEUMAN: [laugh] So that was their opinion of my French.

ZIERLER: OK, so French immersion was more like—that was the goal; that wasn't exactly what you attained.

NEUMAN: Yeah. I think—I mean, I did better than that. I think they—the French are particular about things.

ZIERLER: Of course. And you had I guess Canadian French, which was—

NEUMAN: No, see, at least I had Parisian French, so I wasn't—

ZIERLER: Oh, really?

NEUMAN: —I didn't learn Québécois. And so I had nominally Parisian French.

ZIERLER: Which means what? That the teachers in Quebec were—they had their own French background?

NEUMAN: Yeah, so basically what happened was Quebec separated from France in the 17th, 18th century, and so the French there is just very different. But when I was learning in the French immersion program, they made a big deal about sort of teaching what they call sort of standard French, or what they call Parisian French. Which is ironic, because actually in Paris at the time, there was a sort of slang that gets spoken, and it took me months to understand the students, because they spoke this slang, and it was like another language. In fact, friends of mine came who were, quote unquote, "perfect French speakers," and we would go out, and they would just be like, "What are these people saying?" They had no idea. The language was so—the slang was so deep, in some sense. It was like an argot, they call it. It was so deep that it was hard to understand for a native French speaker. But yeah, so my French was good enough. I caught up. But just the intellectual level was astonishing. And my dad and I would—he would help me with math in particular. It was just unreal. And this is the equivalent of grade ten. And interestingly, some of that math—I remember—I was a double major at Berkeley. So I'm jumping ahead, but I was a math and physics major—yeah, applied math and physics at Berkeley. And I was a senior taking a sort of upper division linear algebra, and all of a sudden like halfway through the year, I realize, "Oh, I've seen this before. Oh, I know all this."

ZIERLER: [laugh]

NEUMAN: "Yeah, I did this in grade ten."

ZIERLER: From high school. [laugh]

NEUMAN: In high school. In Paris. [laugh]

ZIERLER: [laugh] Wow.

NEUMAN: Yeah, yeah. And as a result of that—so over the course of this year, I really—and I really credit this with rescuing me. Really it taught me how to work. It taught me what expectations were. I worked my tail off!

ZIERLER: Now, the dyslexia is conquered at this point, or this is always like a challenge in the back of your mind?

NEUMAN: Always a challenge, yeah. And I think part of the reason I ended up sort of focusing on math and physics was because it didn't involve as much reading. And I always struggled with reading and writing.

ZIERLER: Forgive me, but does dyslexia have a numerical issue as well?

NEUMAN: It can, but typically it's more sort of reading. And there's very specific—I think the classic thing is like long words—I can see the beginning and the end, and then I actually miss sort of everything in the middle. And in fact, ironically—

ZIERLER: But with equations, that's not an issue?

NEUMAN: Less of an issue, yeah. Ironically—so no one had ever really diagnosed my dyslexia, so I couldn't read but people thought I had some general like learning disability. And it was clearly—I could do other things. I wasn't—I guess I could—it was clear I could—my speech was—actually, I didn't speak for a long time, either, too. I was three years old before I uttered a word.

ZIERLER: You're in good company with Einstein, right?

NEUMAN: [laugh] Apparently. I don't know.

ZIERLER: [laugh]

NEUMAN: And so the dyslexia was never really diagnosed. And it was actually my French teacher in Paris who said, "You know, I've been looking at all the spelling mistakes you make, and they're not random, and they're highly characteristic of a dyslexic." And so the actual official dyslexic sort of diagnosis came actually when I was in college. Or actually it was in graduate school when they finally like actually did the battery of tests. And so, I mean, it didn't really matter, right? It didn't change anything. And I think one other thing interesting growing up with my dad—so my dad was an early adopter of computer technology. So even in graduate school in the late '60s, he started using computer-based analysis and whatnot. And that was a PDP-11, so it was a refrigerator that sat in the lab, and when you turned it on, you had to manually enter enough code to like get the disk to start running. And before then, it was like tapes, and he talked about punch card readers. I think I had my first drawings were on punch cards. And so as a result, in the house there was a personal computer. So this is in the early '70s, there was a personal computer in the house. So I could type—

ZIERLER: Do you remember the model name?

NEUMAN: It was a TSR-80 [sp].

ZIERLER: OK, yeah.

NEUMAN: Or Exidy Sorcerer , I think was the other one. And I could then type my essays—I could type the word and spellcheck. And I think that *really* helped me.

ZIERLER: That was big for you.

NEUMAN: It was huge for me. And a common question, all the way through, even through college after writing an essay is—oh, typing things—you know, word check and spell check and whatnot—you know, you can figure it out. But in-class essays, a common question would be, “Keir, what was your first language?” [laugh]

ZIERLER: [laugh]

NEUMAN: Just because it was such an awful hash of writing. So I would say by the time I got to Paris—

ZIERLER: And your parents are native English speakers?

NEUMAN: Native English speakers, yeah, yeah, yeah. They're both generations of being in the States. Yeah. So no, it was just basically—I think later on, it was diagnosed as a very punctate but severe learning disability.

ZIERLER: I ask that because I was wondering if Keir is German from like cherry [?] or something like that.

NEUMAN: No, it’s actually—so my name came—they couldn't decide on a name, and they went back and forth, and it turned out a friend of theirs, their son’s name was Keir. It’s actually—it’s originally Scandinavian. The lineage is also back to Scotland, because Keir Hardie was the founder of the Labour Party, actually. And he was a Scottish miner, so proletariat, and he ended up founding the Labour Party. And so it’s a good—in Scotland, there’s Keir Street, and you know, that’s a good Scottish proletariat name.

ZIERLER: And that’s good context to your father’s political leanings and ending up in Canada, probably. [laugh]

NEUMAN: Yes, yes, exactly. Although I think that was just based upon the name. There was no political overtones. But then another interesting thing was—so my dad’s a neuroscientist, and by the time I was born, he decided it was going to be neuroscience. And so my middle name is Cajal, for Ramón y Cajal.

ZIERLER: How do you spell that?

NEUMAN: C-A-J-A-L. So he’s sort of the father of modern neuroscience. And so that was a nice—it was an interesting sort of little—and it turns out later on in life, when I decided to become a biophysicist, my advisor was like, “Your middle name is Cajal? You *have* to do biophysics.”

ZIERLER: [laugh] Right.

NEUMAN: “This is preordained.”

ZIERLER: That’s it. That’s it.

NEUMAN: And so again, just sort of growing up in this sort of—my dad was that kind of scientist. His own child was labeled with—middle name Cajal, at least.

ZIERLER: So getting back to French high school. So you graduate in 12th grade? That’s the system there?

NEUMAN: So I was only there for a year, so I effectively redid grade ten. But then over the course of this year, it turns out a friend of mine had just started—was sort of midway through university, and she looked at what I was doing, and she said, “You know, you're ready to go to university. You're at such a high level here.” So I made a special application to go back to Newfoundland and skip what would have been sort of—

ZIERLER: Eleventh grade?

NEUMAN: Or twelfth grade.

ZIERLER: Twelfth grade.

NEUMAN: I was doing 11th grade—

ZIERLER: But because you did it again, you were in the age range for 12th grade.

NEUMAN: Right, yeah, exactly. I would have gone back to the 12th grade. So I made a special application. I sort of sent in all the curriculum materials and everything else. I did a little bit of extra—I think I wrote some English essays in English class.

ZIERLER: Probably you would have been bored out of your mind.

NEUMAN: Possibly, yes, right. Yeah, exactly. Right. And so I made sort of special application. It was a long convoluted story. Someone sort of had to really go to the bat for me, but they let me in. So I went back to Newfoundland after that year and started college.

ZIERLER: So staying on in France was not something that you were considering? I mean, just to go to university in France?

NEUMAN: Yeah, no, because I would have had to finish high school. In fact, my friend—I made a very good friend there, and he actually asked me. He said, “Why don’t you stay? This would be great. You could live with me. You can stay.” Although I think it would have caused problems for the school. I wasn’t officially at the school. So for example, they were going to have an audit one day, and basically the head of the school had to come and tell me, like, “Just don’t come in tomorrow.”

ZIERLER: [laugh]

NEUMAN: Just, "You're not here, OK?" And then he had to tell the teachers like, "Yeah, Neuman just doesn't exist." So I was not officially on any books. It was like a friend of a friend of a friend. Because the high school in Paris—all the high schools were actually full. When I would go and talk to them, they would have nothing to do with me. "You're a foreigner. You have no rights." And the private schools wouldn't take me, because they were worried about the level of my French and they didn't want to be involved. So I was one of these back room deals that I was eventually let in. And so staying, I contemplated it, but I think it just would have been really difficult. My parents were going back. Obviously for them it was a one-year stint.

ZIERLER: So in choosing colleges, was there an option to continue on in Canada, or were you laser focused on Berkeley?

NEUMAN: No, no, no. So I started in Canada. So basically what happened was I went back to Newfoundland. I was going to go back with my family. And the notion was instead of finishing high school, I should just apply to college. So I did. I applied to college. And I got in at Newfoundland. So I had one year of college in Newfoundland.

ZIERLER: At University of Newfoundland?

NEUMAN: Memorial University of Newfoundland. Yeah, that's right.

ZIERLER: And was this where your father was?

NEUMAN: Yeah, that's where I went to. He taught in medical school there, and I started as an undergraduate there.

ZIERLER: Tuition can't be beat, I assume, right?

NEUMAN: Tuition, yeah. I forget—yeah, it was very, very cheap. I could live at home. And it was just this—not finishing high school. Moving on with my life. And it was another terrible experience.

ZIERLER: Like kind of a continuation of high school?

NEUMAN: Sort of a continuation of high school, but in a way that I feel like—Newfoundland was sort of economically depressed and socially depressed, and in every possible way, sort of a depressed place. And the federal government I think to some extent tried to make up for this so they could—you know, if you could barely get out of high school, they would pay for you to go to college. And what people saw—this was sort of two years of paid partying in the capitol. And so I remember going through college and you'd see the cases of beer after one month would be stacked up eight feet high, 12 feet long, four feet wide. And the company had a special deal worked out. They would come specifically to the campus to pick these up in front of the dorms, for example. And so there was just this sort of antagonistic relationship between the students and the faculty, and I just got caught up in that. And because I was this weird case—I hadn't graduated from high school in Canada, in Newfoundland, and there was one math teacher who just really wouldn't let it go. And so I was banned from this class. I got in, but he decided I wasn't supposed to be there, and he would actually like literally ask me to leave every—so I spent the first month fighting this. And just in general, the whole attitude between students and professors was very tough, sort of. And so I struggled. It was not a great fit.

ZIERLER: So you did one year in Newfoundland?

NEUMAN: One year, right. And then the growing up in Newfoundland, had friends that sailed. Sailing in Newfoundland is spectacular. So I learned how to sail. I got an inland pilot's license. And then my mother's family was all still in California, and there was a family reunion, and I went down for the family reunion, and my uncle had built a boat in California to sail to Florida. And so over the summer, I sailed with them. He realized I could sail. We got along well. He's like, "You know, we need crew. You should just come with us."

ZIERLER: And this is like a through-the-Panama-Canal proposition?

NEUMAN: Exactly. Yeah, that's right. So I was like, "No, no, no." So I go back to Newfoundland. I'm going to start classes again. And literally it was like two weeks after this, I'm back in Newfoundland, and so over the course of like two weeks, my girlfriend breaks up with me, a job that had been promised to me sort of to help pay for college and whatnot falls through, and the very same professor who just despised me when I took that first class—the two math classes I wanted to take that semester were both taught by him. And I just walked in one day, and I look at all this, and I say, "You know what? I'm not doing it." So I took a little bit of money—I had cash to pay for my courses—

ZIERLER: [laugh]

NEUMAN: —I just turned around, I left, I went downstairs and bought a one-way ticket to California. And so at the end of the day—this is how pathetic my life was. My parents were still picking me up, right? I'm 18 years old. So they pick me up. They say, "Well, what classes are you taking?" I said, "Well, actually, I'm going to go to California. I'm going to do the sail." So I made that visit.

ZIERLER: And that was your plan?

NEUMAN: That was my plan.

ZIERLER: Nothing beyond that?

NEUMAN: Nothing beyond that. That's right. No plan whatsoever. And so I just spent the next, I think, month—like I worked, and saved up a little bit more money, and I had a one-way ticket. I flew to California. I stayed with my grandmother, my mother's mother. Worked on the boat with my uncle. And over the next few months—and I got a job selling shoes. Because I had to—I couldn't—anyway. But my dad eventually called, and he's like, "You know, you're 18 years old. You can do whatever you want. I really can't control you." He says, "I cannot live with your mother while you're on a sail. She stopped eating, she stopped sleeping. She's just losing her mind."

ZIERLER: What, because you're throwing your future away, or because this is dangerous?

NEUMAN: No, just dangerous. Yeah. I mean, it was an untested boat. It was my uncle and his wife, who had never really—they were—you know, they built this boat by hand. They were going to make this sail.

ZIERLER: This is like the tailor-made thing for moms to worry about.

NEUMAN: Exactly. Right. And all she did was—she checked out every book in the library about these sails, right?

ZIERLER: [laugh]

NEUMAN: And you don't write sails about things that are just great and easy, right? You write sails about complete disasters, right? Like you barely survive.

ZIERLER: Now, does your uncle have a reputation with your mom that is making her more nervous?

NEUMAN: [laugh] Yes.

ZIERLER: [laugh]

NEUMAN: He's crazy. And she just—right, there's all these stories of him doing these crazy things and surviving by the skin of his teeth. Yeah. And so over the course of the next two, three—several months, I would say—it was pretty clear I just was not going to make that sail. But here I am in California, and I sort of figured I was going to stay. I got a job. I sold shoes. And then—

ZIERLER: And you said you were living with your grandmother?

NEUMAN: That's right. So I lived with my grandmother, my mother's mother.

ZIERLER: And this is where? This is in Berkeley?

NEUMAN: No, no, no, this is in Benicia, so it's in the East Bay of—it's in the Bay Area.

ZIERLER: Small town?

NEUMAN: Very small town, yep. And it's where my mother sort of grew up, halfway. In the same house, actually. Lived with my grandmother. So the sail sort of fell through. I got a job. I needed to do that to establish residency in California. After a year, I went to junior college, so I went to Diablo Valley College. And that was terrific. That was just a fantastic experience. Sort of a reset on everything. So I went in, and I could sort of make up some of the holes I had. Because my sort of educational career had been very varied up to that point. So high school in Paris, and then one year of college in Canada. It was sort of a hodge-podge and a mess. And junior college I felt like was a place where I could really go and apply myself. I went back to the mode of how I was in France and worked incredibly hard. And there was no distractions. I worked a little bit, but I had—

ZIERLER: Demographically, was it a pretty diverse student body?

NEUMAN: No, it was pretty white. It's in a very rich enclave of California. You'd walk in, in the morning, and you'd go through a lot like filled with BMWs and Mercedes Benz and Jaguars. And that was the student lot. And then you got to this other lot that was closer to the campus; it was all like beat-up Toyotas and Hondas.

ZIERLER: That's the faculty's, right?

NEUMAN: That was the faculty lot, yes. But they really focused on education. It was a very well-ranked junior college. And I could really go and apply myself and really shine. I did really well in my classes. But there was a real focus on education. So I could build up my math again.

ZIERLER: So you entered as a sophomore? Did your first year at Newfoundland transfer, or you were more like brand new?

NEUMAN: It was just brand-new, sort of. Yeah. So I just ignored everything I did in Newfoundland. I just sort of started from scratch, essentially. And went through, took—and that's where I really decided, I guess, over my two years there, or first year there, I decided I was going to be a physicist. I hadn't decided at that point. I knew it was going to be either physics or math, maybe, but I decided—just by sort of saying it, like, "Well, I'll do physics."

ZIERLER: Was there a particular class you took or a professor you connected with?

NEUMAN: No, it was just sort of—I just thought about what I wanted to do. And I liked physics. I liked the fact that that it was—I was good at math and physics. Those were the two things I could actually do. Because there was very little reading and writing involved and not much memorization. You had a sort of core set of things you had to know, and then from there, you could sort of figure things out. And that's really where I decided—I remember just sort of deciding—like people would ask me, "What are you going to study?" and I just started saying "physics" without—

ZIERLER: You say it, and you make it happen.

NEUMAN: Exactly. That's right. But that was an extraordinary experience. And I really felt like I could really solidify everything there. And they taught the basics, I felt like. It was a lot of really fundamental teaching. And the people were really—I had one math professor, a couple times actually—really he challenged me. He realized I could do this, and so he took me aside and he said, "OK, look, you're at the top of the class. You can do more." And so he gave me extra projects to work on and sort of pushed me in ways. And we had a deal, like if I did all this extra work, I could skip the exams, and things like that.

ZIERLER: And your parents, for their own reasons, are probably thrilled with these developments. You're not on the boat. You're declaring a major in physics.

NEUMAN: Yeah, exactly. Right. And I think they were really happy to see me get out of Newfoundland. They realized Newfoundland was sort of a backwater. I think they were really happy to see me outside of Newfoundland. I was living with my grandmother, still. Yeah, no, they were thrilled. They really thought that this was—and my dad, for a variety of reasons, thought I was never going to amount to anything; I was just going to waste away. And so yes, here I am in California, all of a sudden, not on the boat, in junior college, and doing really, really well. And eventually, yeah, deciding that I wanted to study physics.

ZIERLER: Now, do you finish the degree at junior college?

NEUMAN: No. So basically, junior college is a—you can get an associate artsdegree, but it was really—so I spent one year there, and then I had already started talking to Berkeley about going there to finish up. So you would transfer, right? That's sort of how it works. And when I first went to Berkeley—I actually talked to them early on, and at Berkeley, they basically said, "Look, you can't transfer in. You can either come as a freshman or as a junior. You can't transfer any other way."

ZIERLER: Huh.

NEUMAN: And the year I did in Newfoundland sort of left me in a sort of intermediate state, and they weren't quite sure how those classes would transfer. So they said, "Just go to junior college." So I went to junior college. After one year of junior college, I applied to Berkeley, and I actually got in. *But*–

ZIERLER: And this is the only school you applied to? This was—

NEUMAN: Only school I applied to.

ZIERLER: You weren't thinking Stanford?

NEUMAN: No.

ZIERLER: You weren't thinking East Coast? This was it.

NEUMAN: No, just perfect. Yep.

ZIERLER: Why? Because it was on your radar? It was there?

NEUMAN: It was on my radar. My dad had been there. I think he encouraged me. And I just—you know, I was pretty naïve. I had just come to California, and it was close by. And there was a real pipeline from where I was to Berkeley. Several of the faculty in math and physics who taught me at junior college were from Berkeley. And it just, yeah, I never thought of—there was no way in the world I could afford it. I was completely independent by this point. So I was working. Everything I was doing on my own. I was living with my grandmother, but everything else, I was sort of supporting myself. There's no way I could have afforded to go to Stanford or any other private school. And it just never crossed my mind. I thought Berkeley was—the physics department was phenomenal. And the math department was phenomenal.

ZIERLER: So you ended up transferring in as a junior?

NEUMAN: Yeah. So then—well, what happened is I applied the first year after one year of junior college, they let me in, and then I went, and I had a really great counselor. She just looked at my whole everything. She's like, "You know, you're just—you're not ready, and you can't—" It was just a matter of like fitting in classes and everything else. She's like, "Just go back and take another year." So I spent two years at junior college, transferred in as a junior. And I realized that the training, the preparation at junior college was actually phenomenal, in terms of particularly math and physics. So ironically—so when I transferred in, I—so they let me in, no problem, and then I'm looking at the course catalog, and I was going to come in and take the last sort of lower division physics class. So there's a freshman series, like A, B, C. And people told me the one thing at Berkeley is you have to be careful because not all the professors speak English all that well, so you want to avoid—so there were three names. It was like Chiao [?], Zettl [?] and Jackson were teaching, right? And I was like, "OK, Jackson." Well, Jackson it turns out was teaching the honors class. And so I just signed up for it, and I turn up the first day, and he looks at me like, "Who the hell are you?" Because he had been teaching the series all the way through, and there was like 12 kids in the class.

ZIERLER: That he has known the whole time.

NEUMAN: That he has known the whole time, right. And this was a big deal. You get into this as a freshman, and it's a very, very top—and then they weed people out, and it's a very challenging class. And he looks at me, and he's like, "You don't belong here." I was like, "Look, I did really well, I think I'm prepared." And so he said, "OK, I'll talk to your junior college professor." So the next week, he sees me, he's like, "OK, I talked to him, and I'll give you a chance." [laugh] And this was a great story—the first exam, I will never forget. There was like 12 of us in this class.

ZIERLER: What was the professor's full name?

NEUMAN: Actually it's Jackson—J.D. Jackson—John Jackson. He wrote the classic text. This is the person who wrote—J.D. Jackson—the E&M text.

ZIERLER: He's *the* J.D. Jackson.

NEUMAN: He's *the* J.D. Jackson. I had no idea, right? I just took it because he was the only clearly English speaker of those three. And I had no idea. I had no idea that this was *the* J.D. Jackson. Exactly. And the class is so hard that the TA basically said, "I can't do the homework. I'm sorry."

ZIERLER: [laugh]

NEUMAN: "I wait for him to write the problem sets, and then I'll—I'll try and like figure out what he said, and then I'll try and teach you." And the second class—this is now—this is sort of freshman physics, right? The second class was the radiating dipole in reterded time. So it was six integrals up on the board, right? And that was day two.

ZIERLER: [laugh]

NEUMAN: And so the first exam in his class—I'll never forget this. This was awesome. I loved—and so there's like 12 or 16 of us in the class, and so you always—curve, Berkeley is always graded on a curve, so they always put the distribution up. And so there's little bump about 90, and then a break, and then it goes down, and it breaks the curve, the histogram is just because—and then there's one—one little score at 10%. That was me. [laugh]

ZIERLER: Wow.

NEUMAN: Yeah. But I stuck it out, and by the end I—

ZIERLER: He didn't kick you out for that.

NEUMAN: He didn't kick me out. No, no, he's just like, "I'm going to let you stay. I don't think—" He told me, he's like, "I don't think it's a good idea, but I'm going to let you stay. It's on you. I don't think you're going to do well." And so the first test, he's like, "Yep, just like I thought, you're floundering. You don't know what you're doing." But again, I just like buckled down. It was like being in France again. Just like worked my tail off. And by the end, he actually—I think I ended up with either an A-minus or a B in the class, and by the end, he took me aside, and he's like, "You know what? You really improved yourself. You actually ended up—I can't give you the highest grade because—"

ZIERLER: Yeah, where you started.

NEUMAN: "Where you started." But he said, "You ended up very near the top of the class."

ZIERLER: Now, this is a dual major, applied math and physics? Or applied math is a subset of the physics major? How did that work?

NEUMAN: What ended up happening is I came in as a pure physics major, and then what ended up happening was Berkeley is a public school; they were struggling with people sort of spending too long. And so I got to a point by the second year there that before I could have finished the major, they would have graduated me solely because of all the units I had. Because I had been at junior college for two years. The one year of university in Newfoundland sort of counted as classes, but didn't satisfy any requirements. But the total units were such that—and so the only way I could stay and finish the major was by doing a double major because they gave you more credits. And so applied math became an easy way of—I was interested in math, and what ended up happening was that the Venn diagram was such that some of my physics classes would count towards applied math, and so that was a way of extending my time there. And I was interested.

ZIERLER: Yeah, and applied math is very useful for physics anyway.

NEUMAN: Absolutely, yeah. And at the time, I think it was sort of—I remember I had this very arrogant sort of sense—I remember in physics class, like, "Oh, all these approximations." Like, "Well, we're just going to approximate this, and it feels like this." And I'm like, "No, no. It should be like math, and math is so pure." And I thought for a while—

ZIERLER: It demanded more precision.

NEUMAN: Yeah, I wanted to be a sort of theorist, and I wanted to say, like, "I'm going to do like really rigorous mathematical approaches to physics through theory." That was my first entry. I thought, "Let's fix all this hand-wavy kind of nonsense." And so then the applied math classes made a lot of sense. And for a while, I was actually better at math. I think math was sort of—it was so pure. I was a little bit better at math. That went away at Berkeley, but—

ZIERLER: Now, did you maintain a relationship with Jackson? Did he put you on lab projects? Or it was just that one class?

NEUMAN: Just that one class, yep.

ZIERLER: Were there other professors that you developed a mentor relationship with?

NEUMAN: Yeah, absolutely. So then I guess it would have been the next year—

ZIERLER: I mean, the next year, you're a senior, at this point.

NEUMAN: Well, yes, but I ended up—so, nominally, yes, but this is where—

ZIERLER: Or like a super-junior kind of thing.

NEUMAN: Yeah, exactly, right. Well, I ended up—I was really sort of—I ended up spending three years at Berkeley, so I really came in more like a sophomore.

ZIERLER: Yeah. So at the end of the day, you really came in like a sophomore—

NEUMAN: Exactly.

ZIERLER: —even though they told you freshman or junior.

NEUMAN: Exactly. So I came in sort of halfway through the sophomore year, and then it was just a lot of classes to take for this, for the physics degree. And so I guess it was the next year, in a lab class—which was interesting—the professor who taught the lab class—really had an affinity. And I realized I just loved the lab class. This was like the senior lab, the electronics lab. Loved it. Loved building the circuits, loved thinking about it. And so actually I spoke with him—this was Roger Falcone—and I spoke with him about doing research, and he was doing laser physics, and I was intrigued.

ZIERLER: Now, were you a tinkerer, or you discovered this talent like right then and there?

NEUMAN: I was a bit of a tinkerer. I would say I wasn't—like growing up, I wasn't a classic—I enjoyed lots of things. I think I was more of a dreamer, actually. Like fantasy and make-believe and sort of exploring things. And I did enjoy taking things apart, but not—

ZIERLER: Which would suggest more that you're on a theoretical track, but not the case, really.

NEUMAN: But not the case, yeah. Because I think once I really—yeah, and I think all the way through, I was thinking about theory, until I really did a lab class. And then also as an undergraduate, it was much easier to do lab, sort of—to get involved doing experiments. The theorists are just—some of the theorists don't even take graduate students, right? You're just bogging them down. And yeah, I was doing math, but I didn't have the chops. And I really enjoyed this professor, and I liked him, and he was sort of young and charismatic, and I enjoyed the class. And I did very well in the class. And I talked to him, and I was like, "Can I just—can I work in the lab?" And so that's where sort of this started, was—so this is Roger Falcone—and doing sort of high field laser physics, where he's doing ultrafast laser physics.

ZIERLER: What's his big research agenda? What is he trying to accomplish at this point?

NEUMAN: So what he was trying to accomplish was basically—he had sort of been one of the pioneers in building these ultrafast systems. He had some of the very first ultrafast systems. Very high power. These were like terawatt sort of—you know. And so it was basically high field atomic physics. So you're asking like laser-matter interactions but where the hydrogen, where the potential of the electron around the hydrogen atom is a perturbation on the field you're applying. And so you're—extreme physics in terms of light-matter interactions, but extreme fields. And so it was things like—the thing I worked on was harmonic generation. So we were generating x-rays, hard x-rays, from light-matter interactions. From a laser pulse, you were generating like the hundredth harmonic. You were generating a high—that was sort of the work we were doing.

ZIERLER: Which had immediate practical value, or this was more theoretical value and then you'll see where it leads?

NEUMAN: There was a notion that there was practical value to generate coherent x-rays, for example. And this has been something that has continued on a little bit. He was one of the very first people to generate terahertz radiation through light-matter interactions. It was a tool—you know, he sort of came from an applied physics background. And it was a tool I think—the notion was it was a tool—you're doing several things. You're looking at both fundamental physics. So again, studying atomic physics is the extreme—extreme physics of atomic physics. So looking at what happens to the electronic states when you're applying these extreme fields. So they were looking at things like stripping electron shells and Auger [?] decay. They were trying to make a sort of recombination laser. There was a notion of perhaps doing—and there's still work on this—like wakefield accelerators. So it turns out you can generate these incredibly high gradients. And plasma physics was another sort of—so I think it was sort of—he had a tool, right, and then exploring what could this tool possibly do. And he was one of the real leaders in this. And so wakefield acceleration was something we were considering, where you get extremely high accelerations on electrons from the interaction with these very short pulses.

ZIERLER: Were there collaborations that he was pursuing with other universities or government or national labs or anything like that?

NEUMAN: Yep, yep, so he had a huge collaboration with Lawrence Livermore Labs. And in fact, so over my time there—so as I finished up, I spent more and more time in the lab, and I really worked in the lab.

ZIERLER: Did you end up writing a thesis?

NEUMAN: I didn't. And the reason was that I was out of units.

ZIERLER: [laugh]

NEUMAN: And so I was constantly like bumping up against like too many units. So I didn't write a—I wanted to, and just the way it worked out, I couldn't do it. The dual major. And I was just not—they wouldn't let me do it. But I worked in the lab, and then as I finished up, I was debating graduate school, because I realized that undergrad is very—you work on homework and that sort of thing, but grad school is a very different thing, right? Being in the lab. And by that time, I had completely switched. I decided I wanted to be an experimentalist. I just loved—I felt like it was Legos. Growing up, I liked—Legos was my real thing. I had massive amount of Legos. And particularly optics I felt like was this game of—

ZIERLER: Putting things together.

NEUMAN: Right. Legos for big people. And also what I liked about the optics was that it felt like it was a combination of experiment and theory. And so most people in the optics field did some of both, so you could really work back and forth. And so that appealed to the theoretical physicist in me, who I liked that aspect, but I realized as soon as I was in the lab I *loved* being in the lab. I loved tinkering. I loved playing and building things, and the satisfaction of building things. I really enjoyed that.

ZIERLER: So health sciences, this is not on your radar yet?

NEUMAN: Not at all. Nope. And I was—atomic physics. So I finish up, and in fact, I took—

ZIERLER: And this is '95, '96?

NEUMAN: No, this is '94. Yep. So I finish up in '94. And I took actually atomic physics with Gene Commins, who was, like, you know—

ZIERLER: Yeah!

NEUMAN: —phenomenal. And he remains an inspiration in terms of a scientist and how you do science.

ZIERLER: What about?

NEUMAN: He just had such an expansive knowledge of so many things, and he was so calm, but just—an intellect without being sort of self-promoting. You just had this sense that he thought deeply about things, and very deeply about things.

ZIERLER: And he was able to communicate those thoughts?

NEUMAN: And he could communicate those thoughts, yeah. Just when you took your class with him, it was just crystal clear. And I always think that that clarity comes from—it's clear in their mind, and then they can communicate that clarity. And it was just—and you sort of were like—I felt like being in presence was like peering into this abyss, right? He was getting 10% of what he knew, and the clarity was just incredible. Somebody would ask a question, and he's like "Well, do you want to know about this? We can stop, I'm willing to go wherever you want to go, but be prepared."

ZIERLER: "But we're going to have to jump in." [laugh]

NEUMAN: "We're going to have to jump in. We could do this, but we're going to have to—" And it was just a real joy and a pleasure to—and someone that passionate about physics, too. I felt like he really cared. And he was angry with me—I hadn't applied for the right programs to do atomic physics, and he was very angry that I hadn't applied to some certain places which had very good atomic physics. But so at the end of this—'94, I graduated. And one, I wanted to sort of figure out, did I really want to go to graduate school? I was always uncertain. And this whole time through, sort of personally, I didn't have a strong like background growing up in terms of doing academics. I had always struggled a bit. And I got to junior college and I did well, but I'm like, "OK, is junior college--?" You know, it's not that big a deal. And I remember distinctly being at Berkeley, like, "OK, I'll keep doing this until they tell me to stop."

ZIERLER: Which they never did.

NEUMAN: Which they never did. Right. But I kept expecting like, OK, I'll go to Berkeley, and they're like, "OK, you're a nice boy. You should do something else." Right? And so at the end of undergrad, I was like, "Well, I think I want to go to grad school. I'm not sure. So I should spend a year." And so I spent a year in Roger's lab working essentially like a grad student. So I taught undergrad classes to get paid, and then I spent that year working on a project. So we built an ultrafast laser, like an oscillator, and we did some experiments on atomic sort of—not really atomic physics. Sort of atomic physics. It was harmonic generation and whatnot.

ZIERLER: No course work, though?

NEUMAN: No course work. No, I was completely done with course work. And then I—in part of this collaboration, then, there was a grad student working at Lawrence Livermore Labs, and I had to go with him and look at projects there. And so I got to see that.

ZIERLER: Did Lawrence Livermore expose you to like bigger labs and bigger stage?

NEUMAN: Yeah, bigger labs, bigger stage. I mean, similar, but yeah, on a bigger stage. Yes, yes. And a different way of doing science, which was interesting. Berkeley is pretty gritty, you know, and everything was kind of a struggle. It was tape and chewing gum. And literally, Roger—also, Roger was the consummate experimentalist. He could just see things, and—he was very bright, and people describe—on his way in, drinking his coffee in the car in the morning, he'd calculate things in his head, and it would be usually within a factor of two. [laugh] I mean, I would spend two days calculating, and be like, "Yep, here's the answer." He'd check it, and he's like, "OK, this is wrong, but I can see—yep." And then he would have been within a factor of two, in his head over coffee in the morning, driving in traffic. And I'm spending two days with books and everything else!

ZIERLER: This is what geniuses do. [laugh]

NEUMAN: Yeah, exactly. But I'll never forget—literally, like we were working on something, and Roger just like takes chewing gum out of his mouth, puts it down and like sticks this thing into it, and literally it was chewing gum, right, to make this work.

ZIERLER: [laugh]

NEUMAN: We did everything ourselves. And then working at Lawrence Livermore Labs was, you know, it's—

ZIERLER: Did you feel the government bureaucracy component of it?

NEUMAN: Absolutely. Yeah, yeah.

ZIERLER: How so?

NEUMAN: And I'll never forget this, because you know, we're working on this thing, and all of a sudden we spring a leak, right? And so everything had to be under high vacuum, because you're recompressing—

ZIERLER: You literally sprung a leak.

NEUMAN: Yeah, literally sprung a leak. And you're working under high vacuum and whatnot. And so the solution—the first solution was like, "Well, it's 5:00. The techs are gone. We'll go home."

ZIERLER: [laugh]

NEUMAN: We were like, "No! No, no, no! That's not how this works!" Right?

ZIERLER: [laugh]

NEUMAN: "We keep going. We fix it. We fix it ourselves." They're like, "What? What's wrong with you?" Like, "The techs are gone. We just—" You know. And then the other astonishing thing was like, "Oh, well, it's a leak? Well, what can you do?" Well, we can look for the leak. "Well, no, we just have another like $50,000 pump. We'll just put another pump on." Right? And like we had one in our whole lab, and this was like my first project was to design this whole like interlock system such that if you lost pressure, you kill that pump, you turn that pump off immediately so you don't kill it. If it comes up to atmosphere, it kills it.

ZIERLER: So you have like a Depression-era mentality, essentially. [laugh]

NEUMAN: Exactly. At Berkeley. And then at Lawrence Livermore, it's like, "Oh, we'll just put two of these on. If two doesn't do it, we'll put three on. Why not?" So it was a very different approach to do science. And big, big science, but also, yeah, bureaucratic. You felt like it was more nine to five. And I really got a sense of that. So I spent that year. And then over that year, I was applying to graduate schools. And again, I thought I was going to do atomic physics. So this was pre Bose-Einstein condensation, and in fact I was very fortunate—the graduate student who really mentored me, Tom Donnelly, was a real mentor at Berkeley, I really felt like he taught me physics. Working with him every day. And I'll never forget, every morning, he's like, "Keir, are you ready to be famous?" That was how he started every day—"Let's do this." Really—I feel like that's who taught me how to do physics. He was tremendous. And a friend of his was in the Ketterle Group at MIT and came to visit. And this was great. So I had built this pump interlock. This is my first project. And when his friend came and he was telling me about, "You know, Keir is in the lab and he did this and that," and then he said, "Oh, and he built this." And he saw that, and he's like, "OK, this is the kind of person we need in the lab." So I applied to MIT. Eventually I got in. And I thought that's what I was going to do. I really thought I was going to do atomic physics.

ZIERLER: Just the one application to MIT?

NEUMAN: No, no, I applied to—again, I didn't know. So I was surprised. So I applied to like 30 schools and did the whole—

ZIERLER: And did you have different mentors who were pushing you in different directions?

NEUMAN: No, it really sort of focused on atomic physics. And so I was in a lab. It was sort of this high field atomic physics. And then Gene Commins had taught me, and I spoke with him, and so he was again very pro me doing atomic physics somewhere. And so that was really what I decided on. And then that last year I was at Berkeley, Steve Block came and talked.

ZIERLER: I've been waiting to get to Steve Block, because all of a sudden, he's going to become a major person in your life.

NEUMAN: Absolutely. Yep! And I had sort of flirted with the idea of biophysics, but at the time, I was sort of naïve. And I looked around at people, and people were doing a lot of like thermodynamic calculations. There was just no passion. Nothing—

ZIERLER: And it wasn't nearly as well defined a discipline as it is now, also.

NEUMAN: Right, absolutely. It was early days. And I hadn't found any of these key players. And I had sort of looked at it, and I thought, "Well, maybe it would be interesting to do some biophysics. I don't know." I was sort of feeling a sterility in physics, I guess.

ZIERLER: Interesting.

NEUMAN: And also the fact that I sort of realized that like anything I could measure, there was some theorist somewhere who could like calculate it for me right? They just hadn't bothered yet, but I'd probably show them some data, and it's like, "Yeah, I can probably calculate that. Yep, yep." I felt like we were constrained by—a victim of our own success. It was harder to push on frontiers. And you could do experiments, but you were still living within this sort of bubble of the theory was pretty good for most things. And so Steve Block came and talked, and I just saw that talk, and I just fell in love. And it was this beautiful combination of—you know, he was using tools from atomic physics—optical trapping, obviously—or he was studying his molecular motors. And then there was this interesting statistics. So this was the time when he was doing this nice fluctuation analysis. And so this comes back to like again, single channel recording. How do you go from noise to puncta. When you talk about like noise in electronic circuits, it's the same sort of thing. It's because you have a discrete quanta and the noise tells you about that quanta and tells you—right, the noise will tell you some fundamental limits about what's happening. And so Steve was doing this beautiful work trapping beads with kinesin on them. So there was like the physics component of—sort of atomic physics of optical trapping and manipulation, and then there was biology. And then there was this nice mathematical component where he was taking the noise, basically the variance, and the variance was teaching you about sort of fundamental step size and how they step and how they consume ATP, basically. And so it's this beautiful combination. And Steve is just a phenomenal orator. I always tell people, "Go see Steve talk." He's just a master. And I can't tell you the number of people who are doing biophysics who came to the same realization, saw Steve talk, and said, "I want to do that."

ZIERLER: Oh, wow.

NEUMAN: Yeah.

ZIERLER: Wow.

NEUMAN: And some of us were lucky who got to work with Steve. Other people worked with other people. But there's a huge swatch of people who saw Steve Block talk and just said, like, "I want to do that."

ZIERLER: "That's it. That's it." And so this clarified your graduate school options.

NEUMAN: Well, it was interesting because it muddied them, in fact, because all of a sudden, I saw Steve Block talk, and I'm like, "Oh, this is amazing." But I was still very committed to sort of this atomic physics, and it came right down to like the last day of decision. So I had been accepted by Princeton where Steve was, and then MIT—and MIT's on the phone, and they were just like upping the ante. Like, "We'll do this. We'll do this. We'll do this." And they kept making it sweeter and sweeter and sweeter. And then I finally—

ZIERLER: Because you were their lab guy. You were their guy that was going to do this for them.

NEUMAN: Right, exactly. And I had this great training, and I had spent a year as a grad student, and we were publishing papers. And Roger, I think, wrote nice letters. And you know, I knew what I was doing. I had built a femtosecond oscillator. So I had some skills, and I think I was a proven quantity, and I think that goes a long way.

ZIERLER: Sure. And as opposed with Princeton, you're sort of jumping into a new field at this point.

NEUMAN: Absolutely. Yep.

ZIERLER: But this also sounds like it was exciting to you, in terms of pushing the boundaries.

NEUMAN: Exactly. And I went back and forth and hemmed and hawed, and I talked—Roger was great. He was very down on biophysics, actually. [laugh]

ZIERLER: Why?

NEUMAN: He just, you know, thought it was too mushy, and it was not enough physics, and what were you going to learn? But he was great, and he just said, "I think Steve would be a good person to work with." And he sort of said, "You could do atomic physics" but, you know, Bose Einstein condensation was achieved that summer. And so I think he sort of pushed me. And I had this feeling that I just all of a sudden—it was more interesting. Biophysics was more interesting. And I finally—I had had the inkling, and then seeing Steve talk, it was like, "This is what I want to do."

ZIERLER: And are you also developing at this point—since the end point is NIH, at some point in this narrative, you get turned on by human health and helping people and things like that? So at this early stage, is that still—it's still not on your radar yet?

NEUMAN: It's still not on my radar. No.

ZIERLER: So what's exciting exactly about it?

NEUMAN: What's exciting is that it's less sterile. It's life, right?

ZIERLER: It's life, but it's not exactly helping people yet.

NEUMAN: Not helping people. No, I'm still very pure, right? Very fundamental, very basic. But it's just the fact that it's—I was starting to feel that like the physics was a little I guess sterile is the way I felt. Like a little—and also this sort of sense of limitation, right? That our theories were so good that I sort of felt like, "What can I offer? As a talented experimentalist, or as a reasonable experimentalist, what can I offer the world?" And I just felt like there wasn't—I couldn't offer that much. Whereas I felt like biology was—

ZIERLER: You mean like if you're not like a Tony Leggett kind of person?

NEUMAN: Yeah.

ZIERLER: If you're not operating on that level, what are you really—how are you pushing the envelope? Is that the basic idea?

NEUMAN: Right. And even—I would say even some of the top flight—when you really come down to it, and maybe I'm being a little harsh, but the very best experimentalists, I feel like they're living in this world that the theorists are ahead of them, and very rarely do we really have a novel experimental finding. Most of the time, it's like, "Oh, this is really interesting" and then somebody's like, "Yep, I can calculate that." So we had a reasonably good understanding of the kind of physics I was interested in. I realized I didn't want to do high-energy. It was too messy. Cosmology I felt like was too—I liked the notion of controlling experiments, doing experiments. Cosmology was sort of observatory.

ZIERLER: It was almost like as an experimentalist, you were kind of like in the infantry. You wanted to be in a different army.

NEUMAN: Yeah, exactly, right. And also there was this sort of sense of sterility. It's hard to explain.

ZIERLER: I get it. I get it.

NEUMAN: I wanted something more mushy, or something more dynamic. And so that was what appealed to me. And then I couldn't figure out an avenue until I saw Steve talk, and I realized that this is it. And it was a perfect combination of both the atomic physics, like this optical trapping, which was stuff that I understood and thought about, combined with biology.

ZIERLER: So but how was your biology background at this point?

NEUMAN: Zero. Zero.

ZIERLER: Yeah, like you didn't know your way around a cell.

NEUMAN: Not at all. I didn't know anything. I was so naïve. I hadn't had a biology course sine *high school*, right? Never.

ZIERLER: And did this give Steve pause—

NEUMAN: Not at all.

ZIERLER: —in terms of taking you?

NEUMAN: Nope, nope.

ZIERLER: So what did he see in you? Was it basically the same as Jackson and that first class? Like, "I'll take you on and see how you do"?

NEUMAN: No. So Steve—it was more complicated. So I apply to Princeton and I get in, and then I write—and I like Princeton because you do rotations, right? I like that idea. Because MIT, one of the problems with MIT is you get accepted to *a lab*. That's it. Lock, stock, barrel, you're done. And so—

ZIERLER: You were already feeling constrained even before MIT at this point.

NEUMAN: Right. So, "OK, I'll go to Princeton." So I write, and I was like, "I really want to work for Steve Block or Will Happer." Will Happer is a great atomic physicist. And they completely ignore me, and I don't work for Steve, and I end up working for an x-ray crystallographer for powder x-ray. Which was a great experience. And then I got a nice introduction to biology, biophysics. I was doing lipid membranes—liquid crystal membrane stuff.

ZIERLER: Now, biophysics was its own department at Princeton?

NEUMAN: No, it was physics.

ZIERLER: Just physics, right.

NEUMAN: Physics, yeah. So basically I was in the physics department, but I wanted to do biophysics.

ZIERLER: Did they have biophysics?

NEUMAN: They had one biophysicist. [laugh]

ZIERLER: But not as a department.

NEUMAN: Two. No. No, no. No department. Nope, not at all.

ZIERLER: So two biophysicists with joint appointments in biology and physics, or just in physics?

NEUMAN: Just in physics, yeah.

ZIERLER: Interesting.

NEUMAN: And you know, Princeton is a very theory-heavy school. And so I joked that as an experimental biophysicist, I was like below the janitor. Because the janitor had a use, right?

ZIERLER: [laugh]

NEUMAN: Like he'd like clean the toilets and stuff. I just took space and oxygen, right?

ZIERLER: [laugh]

NEUMAN: So I spent the first year doing sort of biophysics in terms of this x-ray crystallography stuff. And it didn't float my boat.

ZIERLER: Were you taking biology classes?

NEUMAN: No, not at all. No, all physics.

ZIERLER: So how did you learn the biology?

NEUMAN: On the job training! [laugh] Yep. So—

ZIERLER: Did you ever think like, "Maybe I've got to go sit down with some undergraduates and take a class"?

NEUMAN: Nope. I just—yeah, I was naïve and arrogant, I guess. Sort of a beautiful combination of both.

ZIERLER: [laugh]

NEUMAN: So I learned a little bit, doing sort of this working in this lab doing x-ray—we were doing sort of, yeah, liquid crystal lipids, and there was a little bit of biology mixed in. So I learned a lot and learned from the postdocs. But it really wasn't—I could do it, but didn't float my boat. And then at the end of the year, I wrote to Steve, and I said, "Look, I'm done with my first rotation. I'd really like to work in your lab." And this is classic Steve; he didn't even write back. Zero. But I got an email from someone else who said, "Oh, I saw you're interested." This was Keren Bergman in the electrical engineering department. "You're interested in working with Steve. I have this project. We're collaborating with Steve, and we're going to build an optical trap and test photodamage in bacteria." And so this was an issue—this was early days—this is '95, '96, I guess? So people had been using optical traps but realizing that—and this goes back to Ashkin, who invented it—he had this wonderfully colorful term, opticution—where he would trap a bacteria or something living, and after a few seconds, he would kill it. This was because they were using 488 light. And he realized that you could go to the infrared 1064 nm, and do much less damage.

ZIERLER: And keep it alive.

NEUMAN: Keep it alive, yeah. But Steve—

ZIERLER: And this is a new frontier, in terms of keeping them alive?

NEUMAN: Well, so Art had done this ten years earlier, let's say, but Steve had this really deep insight that, like, "Well, let's figure it out." There might be some sort of—so 1064 was sort of it, right? And OK, we did better at 1064. But Steve had this insight that, "Well, what is the action spectrum, so to speak? Is there an optimum wavelength?" And so this woman Keren was a laser spectroscopist, and so we built in her lab—I built a tunable optical trap, so on a tunable titanium sapphire laser. Again, back to my roots, right? I built ti:saph lasers, so I knew how to do all this. I put it all back together. Built an optical trap with it that I could tune the wavelength. And then Steve had a really beautiful assay that came from his graduate work. He worked with Howard Berg, and they had studied bacterial chemotaxis. And so there was a beautiful system where they could take the bacterial chemotaxis motor, one mutation—so normally the bacterial flagellar motor switches—it spins in a smooth direction, and then it reverses direction, and then it sort of goes chaotic, and then in a smooth direction and swims, and then they tumble. You can delete one protein and you switch it to a smoothly spinning—constantly spins in the same direction.

ZIERLER: Which tells you what?

NEUMAN: Well, so which tells—and the rate of spinning tells you its metabolic health. That has been directly correlated. So it basically—it converts the energy—the proton-motive force across its membrane goes directly into driving this motor.

ZIERLER: And there's a sweet spot—if it spins too fast or too slow, it's a problem?

NEUMAN: No, it's basically just how fast is it spinning is sort of proportional to how healthy it is. And you could also—you could sort of treat it such that the flagella stuck to the glass. So we had this little system where the flagella was stuck to the glass, and basically the tail wagged the dog. So the whole bacteria is spinning around on its flagellar motor. And as I trapped it—so I'd trap it for a few seconds, let it spin, trap it for a few seconds—and you would see it sort of slowly wind down as I was killing it. And so this was with Keren's lab. And so I had never even talked to Steve, and I just started working with her. And then I talked a little bit with Steve, and I started learning how to grow bacteria. I built the optical trap. I started making the measurements.

ZIERLER: So once you really have something to say to Steve, that's when you're building a relationship with him.

NEUMAN: Exactly, that's right. And even then, I was not in Steve's lab, but I could go to his lab meeting. But I think what people told me is that I immediately impressed him, because I came in, and like the protocol for growing bacteria was a bit fuzzy, so I just sat down and spent two weeks, and I figured out exactly how to grow the bacteria to the right phase, and I made all the measurements, and then I built the optical tweezers. Building the optics for me was my strength, and so I could build the optical trap. That was easy in some sense. In fact, I brought some ideas from *real optics*, let's say [laugh] into building the optical trap. And so over the course of that, I guess it was a year or thereabouts, it was interesting—I went from Steve not talking to me, to all of a sudden Steve saying, like, "OK, so your next project [laugh]—this is what you're going to do." And I knew about electronics, and I knew—and I had the right background, and I could speak up in lab meeting. And so I think he saw something in me. And then we talked about it—finally, we sat down and talked, like, "OK." And it was, "What's your middle name?" "Cajal." And at that point, he said—

ZIERLER: "That's it, that's it."

NEUMAN: "It was in the stars. You *have* to be a biophysicist." I mean, this is just clear as day, right? And then it was interesting, because I sort of—in hindsight, I can't believe I even considered this, but the woman, Keren Bergman, this was a side project for her. She was actually a—she came from the optics group at MIT doing communications. So with her, I actually built fiber lasers and did sort of communication lasers. And she was actually very keen for having me join and stay on that. And I debated. Looking back, I can't believe it was a debate at all, but I debated, went back and forth. Roger was a great source of inspiration. I talked to Roger about this. And he said, "Work with Steve. That's the future. Do that." I did that and never looked back.

ZIERLER: Now, as an instrumentalist, when you're doing these optics, is this a question of you're building machines that have never been built before, in order for you to do what you're doing, right?

NEUMAN: That's right.

ZIERLER: So is this a matter of taking things off the shelf and putting them together in novel ways? Are you working with engineers or manufacturers? How are you approaching this?

NEUMAN: Most of this, starting out I would say we're taking stuff off the shelf and putting it together in novel ways. And these optics companies who just make optical components—and so it's a matter of buying the right optical components, putting them all together. There's a little bit of retrofitting or fixing what is existing already.

ZIERLER: But you're not working with the companies or engineers saying, "I know this is what I need, but it doesn't exist. Can you make it?"

NEUMAN: Not really. A little bit later—I think as we got more sophisticated—you know, the earlier optical traps, it was basically, you know—

ZIERLER: It's straightforward?

NEUMAN: Pretty straightforward, yeah. I mean, the fundamental idea is you take a high—a good laser. You need a laser, and you need an objective with a very high numeric aperture. So you need a very steep focus, basically. And those two things make your basic optical trap. And then after that, then you start adding bells and whistles. We did do a little bit of work with manufacturers. So for example, when we first got these piezoelectric stages, turns out—so we were trying to measure things at a nanometer or a sub nanometer, right? And silly things. So they built a stage, and it had this incredible precision, but their analog-to-digital converter didn't have enough bits of resolution actually to give us a nanometer. And so then we went back to them and said, “You need an extra few bits to give us an actual nanometer measurement.” And so there was a little bit of that. But a lot of this early on was really just taking microscopes and go. We did some of our own machining. But it was really—we could borrow the laser technology and the optics technology, and by combining those two in clever ways, we could make all this work.

ZIERLER: And are you working with the engineering people at all, or this is different world?

NEUMAN: No, this is different world. Yep, yep.

ZIERLER: Now, the master’s degree is something that you just sort of get incidental to the PhD?

NEUMAN: Yeah.

ZIERLER: It’s not its own program?

NEUMAN: No, no, no. It’s just—yeah, it’s incidental. So basically the first year at Princeton is sort of you take these two horrendous exams. And even if you fail the second exam, you get a terminal master’s. If you pass the second exam, you get a master’s and then you're on to finish your PhD. And so I sort of worked through all that. That was part of this. So it was a combination of teaching, working with Keren on this sort of trap, on this photodamage. And then after that, Steve really said, “OK—” And it was this interesting thing. He just sort of—we went from not talking to me to, “OK, now this is your next project, and I want you to work on this.” And then in the midst of all this, Steve was recruited to Stanford. And so I sort of just barely was getting things going in his lab, trying to figure out the assay—so we switched from sort of optical trapping of the bacteria, figuring out the photodamage, which we ended up with a lovely result, but there are very specific wavelengths that actually do very high damage to bacteria, and very nearby wavelengths of light that do very little damage. And then I was able to establish that it was probably singlet oxygen you're generating. So we could push sort of—and that research ended up being important for two reasons. One, for people who are interested in doing optical trapping in vivo, we could tell you exactly what wavelengths to use and why. And funny enough, sort of jumping forwards, years later, ten years later, Steve sends me an email and he says, “Congratulations, you're medically relevant.”

ZIERLER: [laugh]

NEUMAN: And I open the email, and someone—you may have heard these advertisements—so somebody found our research—and of course I was focused on the two minima of damage, but there were two very distinct peaks of damage as well. And I said, “Stay away from these.” And somebody had come along and found this, and said, “Well, that’s very interesting. There’s two places where you do severe amounts of damage to bacteria.” And he came up—he tried various things, but he finally—he fell on toenail fungus. And so sometimes on the radio you hear this—there’s advertisements for laser-based toenail fungus treatment, and that was *all* based upon my research with Steve—

ZIERLER: [laugh] You had no idea.

NEUMAN: I had no idea, yeah. And yeah, I never thought—

ZIERLER: You weren’t even thinking about the practical benefits of *doing* damage.

NEUMAN: No, not at all.

ZIERLER: You just wanted to stay away from it.

NEUMAN: I wanted to stay away from it. Right, exactly, exactly. And I remember distinctly people at Princeton had said to Steve, like, “You should patent this.” Right? And various things. And he’s such a—you know, he’s a dyed-in-the-wool—he’s a liberal and a hippie and—you know.

ZIERLER: He’s not making money off this stuff.

NEUMAN: Not making money off this. And he literally took this guy by the scruff, like, “Get out. We do science here! This is complete bullshit! Get out!”

ZIERLER: [laugh]

NEUMAN: And so yeah, so Steve writes—and this guy was great. I had nothing to do with it, but he found our research, and he was very, very laudatory. Like, the papers and his patents and his—even his company had our data on the front of his company, basically. Like, “This this these two wavelengths.” And he said, “I saw this paper from Steve Block and Keir Neuman, and it just like—I realized what to do.” And so yeah, they take basically little clip-on like light guides, they put them on your toes, they shine this laser on it, and it does—it kills the bacteria over time. Or the fungus. It kills the fungus. So yeah.

ZIERLER: Wow. [laugh]

NEUMAN: And Steve of course does all the research, and it’s a four and a half billion dollar a year industry. And you can take drugs, but they tend to be—you can take them only once or twice because they're really hard on your liver, and the cure isn’t great. And so this is sort of non-invasive. And I don’t know how it’s all working out, but that was a funny sort of—

ZIERLER: That’s amazing. [laugh]

NEUMAN: Yeah. Years later, how that panned out.

ZIERLER: So does Steve move on to Stanford?

NEUMAN: Yeah. So Steve moves to Stanford, and it’s—

ZIERLER: Where does this leave you? Are you thinking about following him?

NEUMAN: Oh, yeah, no, I was—in fact, the irony was that—you know, Princeton—I didn't like Princeton. It was really sort of stuck on itself, and it was small, and anyway. If I hadn't worked for Steve, I was already considering just bailing out and going to Stanford anyway.

ZIERLER: But you ended up finishing at Princeton? You finished the dissertation?

NEUMAN: I did. Well, so what happened was I moved with Steve, we rebuilt the lab at Stanford, and that's really where I did all the bulk of my PhD work was at Stanford. And Princeton is perfectly fine with you just withdrawing. In fact, they kick you out after five years anyway. So no matter what, you're no longer a student at Princeton after five years. So they were like, "Fine, do whatever you need to do." And it's all set up such that all I had to do was come back and sort of be there for a few weeks, defend my thesis.

ZIERLER: So when are you moving to Stanford? Like '99, 2000?

NEUMAN: Yeah, '99, 2000, exactly. Yeah, '99, moved to Stanford. And then we built the lab there. And that's really where I built the—you know, I rebuilt the laser or the laser trap, so that's where I really learned how to do it, on a higher level. The first optical trapping was really just building it and making measurements. Now it was really high precision measurements. And this was transcription. So I studied single molecule transcription by RNA polymerase, bacterial RNA polymerase, basically how does it transcribe DNA, how does it move. And so I could set up—I could basically tether the DNA to the surface of the slide, and I'd put the RNA polymerase on a bead, and then as the RNA polymerase moved along, I could apply a force on the RNA polymerase and measure its displacement. And so through this, we discovered a series of pauses. So the RNA polymerase doesn't move continuously. So conventional sort of biochemical notion was that the RNA polymerase just sort of stepwise moves along, so transcribes DNA into RNA, and does so in a sort of continuous fashion. And there was one known pause that would occur where it would sort of stop and it would actually slide backwards a little bit. And so if you sort of imagine an RNA polymerase with an RNA/DNA hybrid, so it's sitting against the DNA and it's making RNA that's complementary to the DNA. The RNA polymerase can move backwards and can push the RNA sort of out of an entry channel, and then the whole thing stops. And that was the only really known pause at the time. And so what my research discovered was that there's a whole series of pauses that are very short that happen sort of everywhere and are not associated with the so-called backtracking. And we could figure that out by applying force and applying load in various directions.

ZIERLER: And this is a whole new field of knowledge?

NEUMAN: This is a whole new field of knowledge. That's right. And so this sort of fundamental pause that we discovered was unknown.

ZIERLER: Which tells you what? What's the larger discovery at play here?

NEUMAN: So the larger discovery is what we hypothesized and which turned out to be the case was that these pauses are probably actually the origin of all the pausing that this bacteria—that these enzymes do, which are important for regulation and important for termination. So we have to stop. You also have to pause. There are for example transcriptional switches and so sometimes you have to pause or slow down to allow the RNA to fold in certain shapes. And so a lot of regulation takes place by this pause. And what we hypothesized was that this was sort of a fundamental pause and that from that, you could go to this so-called backtracking pause, or you could go to other pauses associated with termination and whatnot. And so that was where—so we established a new sort of class of bacterial pausing. Also, the thought was that—so in bacteria in particular, the polymerase and the ribosome are coupled, and so you generate the RNA and then right behind you, the ribosome was right there generating protein. And this notion was these pauses could potentially help coordinate sort of the motion of the RNA polymerase and the ribosome. And so it was, yeah, a new class of pauses that we were discovering, this sort of new biochemical aspect of this. And that was a large part of my thesis, was that work. And subsequently—

ZIERLER: Now, are you working with Steve in the lab? How close is your relationship at this point? He's telling you what to do, or you're self-directed at this point?

NEUMAN: Steve is very hands-off. So he sets up a project, and then he sort of—he supports you, right? So we had funding. He's a very challenging—

ZIERLER: I assume Stanford threw a lot of money at him to get him to come out—

NEUMAN: Yes.

ZIERLER: —and he was able to—the big opportunity there is build his own lab from scratch.

NEUMAN: That's right. That's right.

ZIERLER: Exactly how he wanted.

NEUMAN: That's right. So we had beautiful lab space. We were in a basement, right? We had many, many optics rooms.

ZIERLER: And the culture—you probably feel more at home back in Northern California?

NEUMAN: Absolutely. Loved being back in—

ZIERLER: You're a fish out of water in Princeton and—

NEUMAN: Yes.

ZIERLER: —you're back home, essentially.

NEUMAN: Yeah. Wearing shorts and riding my bike. Yeah, exactly. And loving being there. And also I think that Princeton was a bit—Steve never really fit in well at Princeton. So despite all his success—

ZIERLER: Where did he come from? Where was he before Princeton?

NEUMAN: So he was actually at the Rowland Institute. So he has a funny trajectory. He was a postdoc at Stanford, actually, with Jim Spudich, and that's where he really got excited by optical trapping. He wasn't doing it, but he was really excited by single-molecule approaches. And it was an interesting story—this would have been I guess the early '90s, late '80s? Probably early '90s, I guess. Very early '90s, late '80s. Anyway—

ZIERLER: So he's not that much older than you?

NEUMAN: Well, he's like 15 years older, yeah, so not that much older. And so he finished up with Jim Spudich and then on the job market, and he was proposing these like single-molecule—I want to do optical trapping and I want to—right? He was really excited by single-molecule—

ZIERLER: But he's ahead of his time and probably people are not really understanding what he's after.

NEUMAN: That's right. So two things—he didn't get a job, at all, *and* he was laughed off the stage some places. This is a good story. So he ended up as a Rowland Fellow at Harvard. So Harvard, there's this Rowland Institute for physics, I guess. And so it's sort of not—it's not a faculty position.

ZIERLER: Like a glorified postdoc kind of thing?

NEUMAN: Glorified postdoc with like one—like he could have one independent—he was sort of an independent postdoc, so he could have one graduate student or he ended up with a postdoc. But it's a hunting position. But that's where he published his groundbreaking research on measuring kinesin stepping. And from there, he was then recruited to Princeton with tenure by Stan Leibler in the biology department. So despite all of his success, the physics department would have nothing to do with him.

ZIERLER: They didn't know what to do with him, right.

NEUMAN: They just—again, right, he's just—like he's dirty. He's this dirty—

ZIERLER: That's amazing.

NEUMAN: Yeah. And then the physics department—when I got there, there were two biophysicists, one—partly because I didn't join, no one else joined. The one biophysicist left. So there was one biophysicist at the physics department at Princeton. And Steve Block is across the way. They would have nothing to do with him. As he was leaving, they sort of deigned to make him an adjunct faculty in physics, right? But anyway.

ZIERLER: So what does that tell you about the biology department and physics? What did they see in Steve's research that the physics people did not see?

NEUMAN: I think it was really led by—

ZIERLER: I mean, they gave him tenure right off the bat, so this is a big deal. That doesn't happen.

NEUMAN: Sure, right. But I think this was led by another biophysicist who was in the biology department at Princeton. He really led it. Stan Leibler is a very, very prominent biophysicist, and he could see what Steve had to offer. And I think by that time, Steve was—people were finally realizing that he had really powerful things to say about molecular motors. And so I think they realized that he really broke in on the scene and was now the leader of the field. And so they took that chance. And I think they saw that. But they could see it from the biology side, right? He was really making these fundamental measurements about biology. This is when he started the work on transcription that I sort of ended up carrying on. And so these fundamental motor properties and then applying it to transcription and DNA based motors. He was really leading the charge in this brand-new area. And so I think the biology department could appreciate that, but the physicists were just—they're just not—you know. The hierarchy there is theory, more theory. And then the experiment is to support theory, and nobody was doing biophysical theory, and so he was—nobody cared. And even—anyway. The Princeton physics department is a funny place, right?

ZIERLER: [laugh]

NEUMAN: Because even Dan Tsui won the Nobel Prize for fractional quantum Hall, right?

ZIERLER: Yeah.

NEUMAN: He wasn't good enough to be in the physics department. He was in the electrical engineering department—

ZIERLER: [laugh]

NEUMAN: —until he wins the Nobel Prize, and all of a sudden, oh, he's part of the club. But no, he was in electrical engineering at Princeton.

ZIERLER: Interesting.

NEUMAN: Yeah.

ZIERLER: And at Stanford, this was not the case.

NEUMAN: Stanford is like—a friend of mine describes it like that's like the wild, wild west. Like that's cowboy physics, right? Like, let's do it all. Even Steve Chu was there, an early proponent. And you just had this sense like—it was much more vigorous, much less conservative, much less hidebound, and much more—I felt like they were going for it, right? And so people like Steve were welcomed with open arms and like, "Yeah, let's do this." And there was just this sense of excitement and, "Let's push frontiers." Whereas I felt like Princeton, it was much more sort of a staid and, "Let's be theorists."

ZIERLER: I wonder if the Institute for Advanced Study had something to do with that, too, or the culture of that place and its impact on the department.

NEUMAN: Possibly. But I also think what—Princeton is very incestuous. I remember—so I took the same sort of exams that they took, you know, in the '30s.

ZIERLER: [laugh]

NEUMAN: And I remember—and there was a debate about this, and people would tell me, like, "Well, it was good enough for me in 1925!"

ZIERLER: [laugh]

NEUMAN: "It's good enough for you, goddamit!"

ZIERLER: [laugh]

NEUMAN: And really they had this bad rep…I think they have a bad—they took a lot of their own, and I think that just leads to this sort of—you don't have fresh blood, and so you just propagate the same thing. Whereas if you're taking people from different places, you get some fresh ideas. And so I feel like there was this inertia and this momentum that they had a hard time escaping.

ZIERLER: And then I had a friend at Princeton, and I remember visiting and feeling that, just at the eating clubs.

NEUMAN: Yeah. Oh, yeah.

ZIERLER: But it's amazing to hear how this bubbles up into the departments.

NEUMAN: Yes, that's right.

ZIERLER: It's amazing.

NEUMAN: Yep, yep, yep. And I think particularly Princeton physics is—you know, and the trouble is—they're like, "We're the best, and so why would we take anybody from—?" Like Harvard is a lower institution, right? Like, "Why would we possibly take a graduate from Harvard when we can take our own graduates?" But then it just creates this sort of incestuous—and I think it's unhealthy.

ZIERLER: So you and Steve both couldn't get out of there fast enough, essentially.

NEUMAN: Essentially, yeah.

ZIERLER: And so you defend. What's your dissertation?

NEUMAN: So my dissertation is basically—so it ended up being sort of mostly this optical trapping of transcription. So we measure—and really what it came down to was discovering these short transcriptional pauses that had nothing to do—so the only pauses that had been known up to that point was the so-called backtracking pauses. And what was nice about the optical trapping is I could apply force. And what force allows you to do is really probe with high sensitivity anything involving motion. And so if you think about what's happening in these backtracking pauses, you're expecting them to slip backwards. And so if I'm pulling backwards, and the enzyme slips backwards, now to move forwards again, not only does it have to overcome whatever the intrinsic energy, but obviously the force—the work—it has to do work against me pulling against it. And so this is an exquisite tool of sort of probing these very fine motions that could be much below what you could see. Because I'm altering the thermodynamics of the property, not necessarily—so even if I can't see it mechanically, I can see it thermodynamically or kinetically. And so we could rule out these backtracking pauses to an extraordinary degree. The model in the field was like any pauses were backtrack pauses, and through these mechanical measurements, I could say, "No, there's no back tracking pauses. None of these pauses are backtracking." My colleagues who came behind me at Stanford could show there were some backtracking pauses. They were very rare. And very long lived.

ZIERLER: Which upended your theory or added to it?

NEUMAN: Added to it. And in fact—and then someone that came after me who I sort of helped supervise and I ended up sort of being part of this work was that then we could really show that there was a sequence context to this. And then sort of out of my work, eventually what emerged over the next sort of decade is that in fact—we can think of the pausing we discovered in terms of an elemental pause. If you think about a pathway where the enzyme is moving along and then it stops—and that's what I discovered, this very brief pause. And then out of that brief pause, you have a different family of what can happen. You can either go back and start moving again, or you can enter one of these longer pauses. And so this is what we ended up terming the ubiquitous pausing, later termed elemental pausing—so this was like the first step in a whole family of different pauses that are important for regulation, for termination, for other regulation of this enzyme, are all happening at this sort of fundamental step. And that was really the discovery of my thesis.

ZIERLER: And who's on your committee?

NEUMAN: So my committee—well, since I really did all the work at Stanford, nobody. [laugh] I was an independent agent. I was—

ZIERLER: Did you go back to Princeton to defend?

NEUMAN: I did.

ZIERLER: Did Steve go with you?

NEUMAN: Yeah, Steve did turn up. And there's a great story. So I defended my thesis in 2002, in the summer. And this was right as the Schön case was breaking.

ZIERLER: Oh, yeah.

NEUMAN: And I was at Princeton, and a friend of Steve's,

Lydia Sohn , was there. And basically I needed a place to like camp out, because I had to be there for several weeks. I had to like submit a thesis and then there was a two-week delay, and I had to be there. So I was there for like a month or six weeks or something. She was very kind. She gave me space in her lab. She was on my committee. She was intimately connected in this whole thing. She was one of the people that broke this case open and exposed it. So I'm in her lab, and she's pulling out her hair. This is right when this stuff is coming out.

ZIERLER: Do you know what's going on, or you're—?

NEUMAN: I do, yeah, because I was getting it from her. And so Steve turns up like the day before my defense, and so I had sort of a characteristic—you know, like a Boltzmann distribution curve where applying force on something, and it's slowing down. So it's sort of a standard curve where it saturates, and then it sort of rolls off, and then it goes from one down to zero through an exponential kind of process. And like a saturating exponential thing, sort of a Boltzmann kind of distribution. And Schön's fake data had a similar flavor. And so Steve took my data, and just to be bad—and he sort of manipulated my data and put it on top of some of Schön's like fake data, and he's like, "Oh, look, your data—" My data matches the Schön curve. And so he gives me the slides. He says, "You have to put this in your defense." Like, "Haha, that's really funny, Steve." And so it's the day before my defense, and we're going through it, and he says, "I want to see your slides. Let's go through your slides quickly." So we go through, and he's like, "Where's the slide I gave you?" I'm like, "Oh, Steve, no, no, that was a joke." He's like, "No, you've got to put that in there. That's gonna be in your—"

ZIERLER: [laugh]

NEUMAN: [laugh]

ZIERLER: What's your response at this point? You're freaking out?

NEUMAN: I was like, "Are you kidding me?" Yeah, like, "I can't do this." And he's like, "You're going to put the goddamn slide in there. Make it so."

ZIERLER: Whoa.

NEUMAN: So I put it in.

ZIERLER: What are you thinking he's thinking at this point?

NEUMAN: He's just—I mean, he's—you know, he—he's a force of nature, right, and at some point, you just—you can't—right? And I was intimidated by him, and I was like, "OK." And he was like mad. He was like, "No, you're going to do this." And so I put it in.

ZIERLER: Are you thinking this is going to jeopardize your defense?

NEUMAN: I thought it was inappropriate, but I figured—at some point you realize—Princeton has these two horrible exams, and I think pretty much—and the way the thesis works, you submit your thesis, there's a two week sort of comment period. That comment period closes before your defense. And so unless they can derail you at your defense, your thesis is solid. You're basically done. And so I sort of knew that, in some sense. I wasn't that worried. I just thought like "This is inappropriate." But if Steve's really going to jump up and down about it, I'd do it, I'd put it in. And so the other people on my thesis committee were Bill Bialek, who's actually a theorist, who had come after we left, and joined from NEC, so he was a biophysical theorist. And then Igor Klebanov was a theorist. I needed somebody for a theorist who was independent of everything else. He was the other person. But very small—actually, but, I was incredibly fortunate—sort of an aside—so when I was working on the photodamage project, this had sort of originated from Art Ashkin. He had looked at this. And Steve said, "You should call Art." And he had been retired from Bell Labs. I'm like, "Oh, I can't do that." Steve's like, "Just call him." So I called up Art Ashkin, when I was still at Princeton, and three, four hours later, [laugh] I had had his whole life story, and he told me everything. It was just a wonderful conversation with Art. And I checked in with him a few times. So for my defense, I knew he was living in New Jersey, and I wrote to him, and I said, "Art, I'm going to be defending my thesis. It would be a thrill if you would come and hear my thesis." So of course I wasn't a student there any longer, so I came back. The committee was incredibly small. And someone said, "Oh, Keir, there's this guy wandering around the department with a woman, and who could that be?" Turns out Art Ashkin came. Didn't tell me.

ZIERLER: Wow.

NEUMAN: But he was like one of five people who sat in my defense. And that was a thrill.

ZIERLER: That's great.

NEUMAN: And I have a picture of Steve—

ZIERLER: Boost of confidence for you, too, at that moment, right?

NEUMAN: Yeah, I guess a boost of confidence, but just like what a thrill, you know? This is the guy that created the whole field, and he was there. And it was the summertime. Nobody was there. And so that was a real—it was really lovely. Anyway, so yeah, I'm giving my thesis defense, and indeed I get to the slide, and I show like, "OK, here's my data" and then the next slide is the one Steve made me put in. And like, "Well, my data fits the Schön standard curve." And Lydia who was on my committee, she looks up, she threw something at me. [laugh] She took her pen and threw it at me. In my defense! Anyway! And then we finished up and it was fine.

ZIERLER: And that was the extent of your relationship with that controversy.

NEUMAN: Yeah, exactly. Then I was done.

ZIERLER: So you never got any more input from Steve as to why he made you put this in?

NEUMAN: No, he just thought it was funny. And he knew Lydia was involved, and Lydia was really deeply involved in this whole process. So I think it was more for her sake than for anything. And just—Steve was a prankster. He was a lovely prankster. And so this was just, you know, making it fun. He enjoyed it. And so that was—

ZIERLER: OK, that's interesting.

NEUMAN: —that was that.

ZIERLER: So postdoc, back to Stanford?

NEUMAN: Back to Stanford, right.

ZIERLER: You feel like you still have more work to do with Steve is the idea?

NEUMAN: More work to do with Steve, right. And then also my girlfriend at the time was finishing up, and so it was like a year for her to finish up.

ZIERLER: She was at Stanford?

NEUMAN: She was also at Stanford, yeah. And there was stuff to finish, right? That paper wasn't done yet, and there was other things to finish up. And so, right, I worked it out with Steve. So one year postdoc with Steve, finishing up that paper and some other work, getting some other work sort of up and going, passing on the knowledge, if you will. And over the course of this, what I realized was that RNA polymerase is not really—so if you think about the structure of DNA, it's a helical structure, and you've got something that's sort of walking along one of the two strands reading it. And if you think about it, it's not—we treat it like a linear motor, so I'm pulling on it, I'm applying a load on this and asking what happens. And over time, it dawned on me—this is not a linear motor; this is a rotary motor. It must be stepping around the helical axis. And so a large part of my work, or a fraction of my work at Stanford was spent trying to think about, "Can I see this directly? Can I see the rotation?" And that led me down the road of—

ZIERLER: So you theorized that it was a rotary motor—

NEUMAN: Yeah.

ZIERLER: —before you saw that it was a rotary motor.

NEUMAN: That's right, that's right. And it sort of made sense to me, but I was struggling with the "Can I make this work?" And I tried various things, and none of it worked. And then someone else in Japan finally did show—they could see this—at the single-molecule level, she could show that it actually was a rotary motor. But this led me to think about DNA topology and sort of the winding of DNA and—

ZIERLER: Topology?

NEUMAN: Topology.

ZIERLER: Topology, uh-huh.

NEUMAN: Right. And so how does DNA—so as soon as you start winding things around DNA, the question is like, does this wind, or does the DNA get wound up? And so you can wind up DNA, and that's a whole field of sort of how DNA is wound up or underwound is what's called DNA topology. And it sort of got me thinking about this. And then as I'm finishing up the postdoc with Steve thinking about what to do next for a real postdoc, I decided that I—like the postdoc is this finite time where you have to do something else. You can't stay. You have to do something else after that. And I thought, "Why not see the world?"

ZIERLER: And particularly a part of the world you're very well acquainted with.

NEUMAN: Well, but at the time, it wasn't even—it was just like, "Let's go someplace else." So I spoke and I convinced my girlfriend and eventually wife that, "Let's think about doing a postdoc someplace else."

ZIERLER: And how's this lining up with her timeline? She's going to do her own postdoc at this point?

NEUMAN: That's right. So she's finishing up, right? That's why I spent that year. So she's finishing up, she's graduating, and so we both applied to postdocs together.

ZIERLER: What's her field?

NEUMAN: Her field was chemical engineering. And I sort of left it up to her. I sort of secretly wanted Paris because I knew this lab in Paris. I'd met them, I knew them, I'd reviewed their papers. And it was just—and so coincidentally, just by happenchance, she also found a lab in Paris that was great. And so we both applied, and we said, like, "We're going to apply each to one lab [laugh]. If it works, we go. If it doesn't work, we'll do the conventional thing and stay in the States." And at the time it was interesting—people at Stanford gave me a really hard time about this. They said, "You're throwing away your life. You're ruining your career. This is nonsense."

ZIERLER: And your response is, "The hardest I ever worked was when I was in tenth grade." [laugh]

NEUMAN: Yeah, exactly. I was just like, "You know, it's my life. I'm going to—" I feel like we have to do interesting things in life. And so—

ZIERLER: So Human Frontier?

NEUMAN: Yes.

ZIERLER: This is a program? What is this?

NEUMAN: This is a funding agency. It was started by the Japanese government, but they got buy-in from several governments around the world, and it fosters—it's an international collaboration. And so what they want—

ZIERLER: And it's its own thing? It's not UN or nothing like that?

NEUMAN: No, it's entirely its own thing, but it's an extraordinary institution. It's really phenomenal.

ZIERLER: Where's the headquarters?

NEUMAN: The headquarters is in Strasbourg, France. And basically the idea is that—what they like—so they fund at various levels, but the real idea is international collaboration. They want to see people collaborating around the world. And they also like to see people moving among fields. And so normally I wasn't really moving among fields, but I think—and they liked the fact that I was coming from the States—I was Canadian, and I was coming from the States and going to Europe, and I was going to sort of apply physics to sort of biological problems. They liked that sort of transition. So they funded me. So I found the lab in Paris that had really sort of I think developed this technique—it was complementary—it's optical tweezers, and you focus a laser tightly. You manipulate a small dielectric particle. If you apply force, you can measure displacement. That was my graduate work. And the lab in Paris that was started by Vincent Croquette and David Bensimon who pioneered this technique, what they called—referred to as magnetic tweezers, where you take a magnetic particle, you manipulate it in a magnetic field and apply force, and you measure displacement. But the unique difference was, among many, is that you could now—because the magnetic particle is polarized, I can rotate the magnetic field, I can rotate the particle. And that was very challenging to do. It can be done with optical trapping but it's challenging and sort of messy. And now I have a way—so I put this on a piece of DNA, I can now wind up the piece of DNA. And this is this so-called topology. And so they really introduced this whole field of studying DNA topology at the single molecule level. So you can take a single molecule of DNA. And whereas like Steve and others could pull on it and stretch it, and ask, "Does it get longer or shorter?" or as an enzyme moves on it, has a change, now this French lab had been able to do that, *plus* they could wind up the DNA and ask, "How do these enzymes unwind DNA ??" Or, "How do enzymes wind DNA ?" Or what's the relationship between the winding of the DNA and the mechanical properties.

ZIERLER: So these new capacities, are there advances in optics that are taking place that you're taking advantage of? Or what's new here?

NEUMAN: They had sort of established this, and in some sense it was a forced thing, because they actually didn't have the same access to like advanced optics. And so it's actually very simple. It's literally a pair of magnets and a microscope. [laugh] So it's a much simpler, much more robust in many respects. And again it's this notion of making do with what you've got and being clever rather than being sort of able to buy your way out of trouble. And this is something I learned—

ZIERLER: Culturally, is there like a uniquely French way that this is happening?

NEUMAN: I would say there is a cultural element. I also think what I realized is that particularly Vincent Croquette is just an experimental genius. And he's someone who prizes simplicity and elegance over complexity and byzantine baroque kinds of things. And he has deep insights but also the ability to realize—to make a lot of what he has. And so he really developed this technique. And he sort of saw people like Steve [Block] and Steve Chu manipulating DNA, and he's thinking to himself, like, "Well, I can't set up these fancy lasers. I can't do all the stuff that they can do. What can I do?" And he thought hard about it, and he said, "Well, I can use magnets. Magnetic particles." And so he developed this. And then he realized he had this insight that he could also twist them up. And so he really created a whole field of single-molecule topology. Whole cloth. Really, it's out of his mind.

ZIERLER: What is in the molecules that's responding to the magnets?

NEUMAN: Basically what you've done is you've taken the DNA, and you attach a magnetic particle to one end of the DNA. And *that's* what responds to the magnet. So it's just a little tiny magnetic particle, it's one micron—also called superparamagnetic bead—that you can polarize with the external magnetic field—

ZIERLER: So this is something external to the DNA.

NEUMAN: External, yeah. So this is something that you buy. And we sort of repurposed—biologists use this all the time to basically attach something to this bead, and then pull it down with the magnet. So they use it for affinity capture, right? So they stick their molecule of interest to this bead, and they can then purify that away by using a magnet. And we repurpose it—we take that same bead and instead of—we now attach it one at a time on the end of a piece of DNA, and then the other end of the DNA is attached to a microscope slide, for example, and then just permanent magnets, just like Radio Shack magnets [laugh], you put them above the slide, you get them very, very close, and they will pull up on this bead. And then the unique thing is I then set it up in configurations that I could rotate the magnets, then I rotate the bead, and now I have a little wind-up toy, basically. So if I set things up properly, I can take my DNA and just like a hose, I twist the DNA, and the DNA will eventually buckle and form a plectoneme just like taking—we don't have telephone cords anymore, but your iPhone charging cable, if you twist it up, it will form a plectoneme. And it turns out—so that changes the mechanical properties of the DNA. It changes the extension, which I could measure very accurately. And also techniques that were developed by Vincent using optical approaches. Very simple optical approaches. No fancy lasers, no nothing, just sort of really relying upon the principles of optics and interference, basically, diffraction.

ZIERLER: So this is more like a purely physics kind of environment that you're in right now, without the bells and whistles?

NEUMAN: Yeah, it's purely physics, *but* it gives you access to these sort of very important aspects of DNA that are important in the cell, in fact, and that are hard to address in other approaches. And I guess coming back to the question you had asked earlier—when I really—

ZIERLER: Right, this is my next question. Is it happening now?

NEUMAN: Yeah, yeah. So it really happened over graduate school, I think. I came in as a physicist, and I really wanted to build optical traps, and it was really coming from atomic physics. I was like a builder, right, and I could build things. I wanted to do physics. But then—

ZIERLER: I mean, you're working up close with DNA every day. It's like inevitable this is where this is headed, right?

NEUMAN: Well, yes and no, because I think—a lot of people work with DNA because it's a convenient polymer. And I always refer to biophysicists as sort of "little b, big P" biophysics—and people take a biological polymer and they do physics with it, and it's really physics, right? Or there's "Big B, little p" where you're doing biology but happen to be using physics. And that's really where I went. So I looked at all this, and I realized that biology is fascinating, and—

ZIERLER: So this fork in the road, this decision that you make, this is happening in France?

NEUMAN: No, it's really over graduate school. I think over the graduate school, I really realized that what's interesting is the biology. And I'm learning a lot of biology, on-the-job training, right? So I just taught myself. It was all reading and just reading textbooks, reading literature. And Steve's big point is that physics has got a lot of depth. You start from the bottom and you build your way up in physics. And he said it was much easier to take a physicist who understood—

ZIERLER: The foundation.

NEUMAN: —the foundations. The optics, the math, the quantum mechanics, the things you had to know, the statistical mechanics, math and whatnot. And also the technical aspects. You could teach them biology. Because biology—I don't mean to take anything away from it, but it's a very sort of broad enterprise, and you can jump in at any point and sort of learn what you need to know, but it's incredibly broad. And I think the challenge of biology is connecting these broad fields together. But so I jumped in as a physicist but then realized very quickly that the real questions in my mind in science right now are biology. And what struck me was I could jump in, and in a matter of months or a year, make measurements that I was right on the cutting edge of exactly what was going on and what we knew about this important biological process, transcription, right? We discovered these pauses. Nobody had had any idea about these. And we were using physical tools, and sort of going about this in a quantitative sense, but we were exposing new biology routinely, and some new physics along the way in some of these things. So that really inspired me, and I really decided that the exciting sort of science to be done was in biology using these physical tools. And so that was the switch, I think, was over graduate school, in terms of like, "What am I really interested in? I'm actually interested in studying biology, but doing so with physical tools." And then going to Paris was sort of this notion of now being able to understand how DNA twists and is sort of twisted and untwisted. And this is critically important in cells. All your DNA in cells is not sort of linear relaxed DNA; it's actually twisted up and wound up around things. And that plays an important role in how everything works, and yet it's hard to study. Most experiments done on enzymes or other things in biology are done on sort of short linear pieces of DNA. That's not at all what they see in the cell. So now we have this tool, the sort of magnetic tweezers as we say, that allows me to twist up DNA. I can twist it up, I can pull on it, and I can now probe how do these enzymes work on this different substrate, which is actually closer to what we see in actual cells than most biology can do. Which is sort of ironic. Sometimes biologists will say, "Well, it's this tortured system, and it's biophysics, and what are we learning?" And then I can push back and say, "Actually, my system looks a lot closer to what's happening in the cell than your system."

ZIERLER: So at this point, are you already starting to see how intellectually your work is going to lead to better understanding of like metastasizing cancer and heart problems and things like that? Or you're still—you're not there yet?

NEUMAN: No, I'm still—it was coming to the NIH with some of that change, but I still—fundamentally, we're doing very basic science, but I think what changed was my interest became much more biology and much less physics, and I started seeing physics as a tool. And there's still some interesting physical problems we work on, but I really saw the interesting problems—that what really was motivating me was biology. And so that, I would say, over the course of my time there, I got more and more steeped in the biology. Again, biophysics, but more on the biological side. I tried to take physics to understand biology. And so when it came time to decide on jobs, I think coming to the NIH made sense for a couple reasons.

ZIERLER: You're in Paris for three years?

NEUMAN: For three years, that's right.

ZIERLER: Are you publishing? Is it one project that you finish and that's why you're done at three years? Or what's the timing there?

NEUMAN: So the timing—actually I didn't—the work I did, I didn't even publish. So what happened—I'm there for two years, and people—and I was still publishing work from my graduate work, and from my postdoc work with Steve. And these were early days in single molecule, still, and a lot of people in the field said, "You should apply." And again, I was shocked. The same mentality—oh, they're going to say like, "Well, you're a nice boy, but no. You're not ready." And I didn't know what I was going to do. I just wanted to do a postdoc, and then we'll figure it out. I really didn't know. But people said—after two years, they said, "You should apply." I was like, "Really? A, I haven't published anything. And B, really? Am I competitive?"

ZIERLER: Are you married at this point? When does that happen?

NEUMAN: Yes, I'm married. Yes, that's right.

ZIERLER: You married in Paris?

NEUMAN: Right before going to Paris.

ZIERLER: So your wife, she has her considerations as well during this?

NEUMAN: Right. But so I say, "OK, I'll apply." So after two years there, no publications. I have something in process and I have a story but no publications. And so I apply. And I was incredibly fortunate—again, Steve was an incredible advocate. I got a job interview for someplace I didn't apply. And I asked, like, "Well, this is very nice." So I get an email, like "We want you to come and interview." And I'm like, "This is really nice. I didn't apply." And the guy writes back, and he's like, "Yeah, I know, but I sat on a plane next to Steve Block. We flew across the country. When I got off the plane, it was drilled into my head like the first thing I did was I came here and I wrote to you to ask you to apply." [laugh]

ZIERLER: And where was he from? Where was he coming from?

NEUMAN: This was Rutgers. But Steve was really incredibly helpful, right? Remarkable mentorship. And I think there's things he has done behind the scenes that I don't even know.

ZIERLER: So you're in regular contact with him while you're in Paris.

NEUMAN: Yes. Because we were finishing papers. And some of the work I had sort of started was being finished up, and I was intimately connected with that—sort of writing papers, and yeah.

ZIERLER: And Bensimon and—did they have opinions about what you should do next? Were they hoping you'd stick around?

NEUMAN: No, no. They were very just—"Take on the world." And they were very generous. So it's always a question when you leave a lab, what do you take, and what do you leave? So I had actually come to the lab—I wrote a proposal to study something that turned out not to work, and unfortunately our collaborator actually died when we were there, when I was there, and so I took on another project. Classic story. This was going to be a six-week project. Well, that was the entirety of my postdoc time there, right?

ZIERLER: [laugh]

NEUMAN: And got me a job. A quick project. Which, sort of again, we rewrote the field, right, so there's—sort of an arch competitor had written a paper and made these claims about something, and we were going to try and measure with more finesse. We were going to put a decimal point on something. That was what we thought. And yet my work showed that it was completely wrong, and he got it all backwards. And so that ended up being my—I dug in on that. But they were very generous. I sort of proposed what I was going to work on, and it turns out they had thought about something similar, but they said, "You know, you take it." And then, "By the way, while you're at it, this other protein that you've been working on, this sort of six-week project"—that had been really their bread and butter; they started this whole field—they're like, "You know, we think we're pretty much done. Take that too." [laugh] "Just go." So they were very generous in terms of intellectually being very generous with giving me things to work on. But when I was looking for jobs, I applied again—I applied 30 job applications or something, a mix of physics and biology departments, and biochemistry, and even chemistry departments.

ZIERLER: Was NIH the only non-traditional academic job you applied to?

NEUMAN: Yeah. And I credit that with someone here, Wei Yang, who's a crystallographer here, who I saw talk many years ago at Stanford and just blew my mind at how terrific she was.

ZIERLER: Is she still here?

NEUMAN: She's still here. Oh, yeah, yeah. She's terrific. And I ran into her at a conference and she said, "When it's time to think about jobs, think about the NIH." And that was the extent of my conversation, but I had such high respect for her that when I saw a job opening at NIH, I thought, "I'll apply." Simply because she said I should. I never thought about it. I never thought I would be here. I really thought I would be either at a physics department or maybe like a biochemistry department, with a biophysical component.

ZIERLER: And industry never crossed your mind?

NEUMAN: No, no. I mean, I really—I think—industry for me would have been a backstop, I think. I just feel like what I do is so fundamental, and I like this sort of notion of just like curiosity driven. I feel like we're really lucky to do this. It's all curiosity driven. And so we can just follow our nose. "Where does this data take us, and where does the science take us?" And the work there again, very fundamental. It's just how these enzymes work. How do these enzymes untwist DNA or twist DNA? How do they respond to that? So I applied. I had several interviews. I had several offers. And what struck me about the NIH was twofold. One, it was a conscious decision to sort of give up on the physics side of things a little bit. So I wasn't going to be in a physics department, and I was giving up that physics side of things, which was a—

ZIERLER: Which was in keeping with the general trend line that you were already on.

NEUMAN: Yeah, you're right. It was, but it was also—you know, I do miss—I don't see talks on gravitational waves, or I don't see talks on interesting atomic physics anymore, or condensed matter physics, which is—you know, that's where I grew up, in some sense. But it was a conscious decision that what really interested me was biology, and that I could come here and learn a lot. And I could also come here with a unique sort of skill set and tool set. I could see this as sort of a playground to come, and being somewhat unique here, there's a lot of people that come to me. And also, I'm a student. And as soon as I got here, the same Wei Yang, in a different institute, her sort of lab and the labs she worked with invited me to participate. And so every week I go spend time there, and I'm learning biology from them. I'm learning right from the cutting edge of what's going on in research. But it has been a learning and education for me. So that's where I really learned biology, I would say, is at the NIH. And I'm still learning. I still have a lot to learn. And so that was a conscious decision at that level. Also I realized in terms of funding and the structure of how things work is that the best way I could describe this is it's a little bit like Bell Labs in the heyday of Bell Labs. This goes back to Art Ashkin. It's where Art Ashkin did his seminal work. And I realized that being here, I was just unfettered, and it was just my imagination.

ZIERLER: You were not going to be writing grant applications all day long.

NEUMAN: I wasn't going to be writing grant applications. I wasn't going to be teaching. And really—and it was just this place where they give you some resources. You know, you have small labs, not a huge lab, where you could just focus on doing science. And that's what really appealed to me.

ZIERLER: Did you understand in those early days about the spirit of collaboration that makes NIH so unique?

NEUMAN: Absolutely. And that's something that was really—I think that's one of the things that I think has really—I have really enjoyed in science in collaboration. So my PhD work was actually a collaboration with Steve Block, who was single-molecule, optical trapping; Jeff Gelles, who's another single molecule person that had done a lot of single molecule transcription work; and also Bob Landick, who was a transcription person. So I really felt like I had three PhD advisors. And I could see how collaboration was just such a beautiful—when done right, it really just adds so much more. And I think physicists in particular, scientists, we all tend to be a little bit introverted, and it's our way of socializing, in some sense.

ZIERLER: [laugh]

NEUMAN: Because we have a connection with these people now, and so then it allows us to talk to people in a way that I can't talk to people on the street. And so I feel like it's a sort of social aspect of science, which is lovely. And so that was something that I really appreciated. I realized that the NIH—and part of me coming here was I realized that I could be at the hub of people wanting to do the kind of work I do, coming to me with problems and saying, "Oh, we have this problem. Can you help us because you have these unique tools and these unique abilities?" And to a large extent, that has been the case.

ZIERLER: And are the people that are coming to you, are they—are you working with MDs? People who are interfacing with patients who have unique challenges that you have solutions for?

NEUMAN: Yep.

ZIERLER: Or at least you're the best approximation for what they can find in terms of help at NIH?

NEUMAN: Yep. So I would say we're—I do work with people who hold MDs, but then again, we tend to be on the very basic side of things. But I do say that being here, I've been exposed to clinical research in a way that I never expected. And so there's one study in particular we've done—I've certainly interfaced with people who are interfacing with patients. Or on the pipeline, let's say. And there are two things we've worked on that are directly related to this. One I think was really compelling to me. So we studied these topoisomerases, and these are enzymes that control DNA topology. So this is how the DNA is overwound and underwound in the cell. And an important aspect of what they do is to manipulate the topology of something, you have to cut it. So like if you take a string, and you wrap it all up, and you tie the ends together, that's topologically closed. No matter how you pull and twist that string, you don't change the topology. To change the topology, you have to cut the string, take it apart, go through some manipulation, then put it back together. And so that process in the cell is very dangerous. Because when you cut DNA, that's a very dangerous situation in the cell.

ZIERLER: You mean dangerous in terms of its prospects to continue living?

NEUMAN: Yes, exactly. So most of what the cell does is work very, very, very hard to repair and prevent cutting the DNA. And so all of a sudden now, you have enzymes that are within you that that's their job is they cut the DNA. And so they're very dangerous. And what people actually here at the NIH realized was that you could poison those enzymes and turn those enzymes into very, very potent killing agents. And so if you're taking something that's intrinsically cutting the DNA and you can prevent it from religating the DNA, or you can make those cuts permanent, then you can kill cells. And that's how bacterial agents work. So ciprofloxacin was very popular in the anthrax scare; it targets topoisomerases and it turns this sort of natural enzyme within the cell into a killing machine by preventing it—it allows it to cut the DNA, and then doesn't allow it to reseal. Similarly, human cancers are treated with very, very potent poisons that are first line chemotherapeutic agents for human cancers, and you target them against cells that have more of these topoisomerases. They're rapidly dividing. And you turn these topoisomerases that are essential for us into very lethal sort of killing machines. So there's a scientist here, Yves Pommier, who's a pharmacologist, he's an MD, he has spent the last 20 years developing new compounds that target a particular topoisomerase, so-called topoisomerase I, in humans, that has been targeted for chemotherapeutic purposes. So I find this work really compelling and lovely. He has developed novel inhibitors. And what you appreciate over a while is that the—not meaning to take it away, but mechanistically, they don't really know what's going on, right? They add this, they see there's more cleavage, it kills the cells, OK. It doesn't do that much damage to people. Let's try—they're in clinical trials right now. But there was a missing component of like actually what are they actually doing at the molecular level. And so working with him and the single molecule method—OK, now twist up the piece of DNA, I could add the enzyme, I could then add this poison, and I could figure out exactly what is the poisoning doing to the actual activity of the enzyme. How is it changing it? And in a really compelling graph, we have our single molecule measurements of one of these aspects that's changing. Sort of how long is this molecule bound, essentially, is what we're measuring. And on the other axis, we have the sort of how toxic is this compound. So we have cell biology measured in our collaborator's lab on sort of one axis, single-molecule measurements on the other axis, and the correlation is perfect. It's one to one. And so we can take the clinical data, the clinically relevant data, and convert—and understand that in a molecular basis. And now we can tell the clinicians, or the people—the pharmacologists—"This is what you want to optimize. One parameter. You optimize this parameter, you will extend killing." And that to me was really compelling. And we were working on these compounds that are in clinical trials, right? So people are in phase two, efficacy trials, at the NIH, and we're studying the same compound at the single-molecule level here in the lab. And that to me was really powerful. Another work with the same investigator—there was a particular—so our mitochondria have their own special version of one of these enzymes. And interestingly, it's not essential, so in mice, you can knock it out, and oh, they're a little bit shaky but they still survive. But we were looking at variations in human populations, in the so-called SNPs, so single-nucleotide polymorphisms. And they had this interesting insight that you can have different polymorphisms, but they never coexist. And so we could then make these mutants ourselves and test them here. And then one of these mutants we made was from a patient sample. So the patient would come in—she had an idiopathic—so an unexplained mitochondrial disease. Clearly, her mitochondria were very sick; they couldn't trace it to anything. There was one mutation in this enzyme, but when they look at this with a standard biochemical assay—you put it in a test tube, you ask what does it do—no effect. So they say, "Well, there's this mutation, but it doesn't seem to have any effect." And in our hands, what we saw was as soon as you sort of stress it a little bit—so we could put a little bit more force, a little bit more torque on this, than they can put in a standard biochemical assay—but I would claim is much more relevant to actually what's happening in the cell—we see this thing completely breaks down. And so we can now attribute sort of a mechanical or a real molecular basis of this disease that this patient presented with, and for the first time associate with what's happening. Why is this enzyme not working in this patient in a way that we could understand mechanistically, from the studies that we did here. So these were two examples where I felt like we're really interfacing very closely with actual biomedical research.

ZIERLER: So that's the diagnostic aspect. Are you also involved in the therapeutic aspects?

NEUMAN: So in the therapeutic aspects, we're sort of—what we're understanding is how do these therapies—what is the molecular basis of how these therapies work? So what they know is that you add this, and the enzyme stops working. And what we can show is sort of at a molecular basis, what is the—so these therapeutic compounds sort of screw up the enzyme in lots of different ways. So some of them make them go faster. Some make them go slower. Some do this, and some do that. And the question was out of this sort of morass of different things that happen, what's actually relevant in terms of killing cells, in terms of clinical efficacy? And this was a measurement we could make to show that of these various things that are happening, it's one particular aspect of this drug interacting with this protein that gives you therapeutic efficacy. So that's where I would say—so as a screening tool, asking about how do these enzymes work, or what's the combination of this drug and this enzyme? What's actually clinically relevant at a molecular scale? That's something we can give some insight to.

ZIERLER: I wonder if you could talk about your understanding of the tenure process here relative to what you might have expected in an academic setting.

NEUMAN: Yep. So tenure here I think by and large is very similar to an academic setting. I would say the subtle differences or important differences—obviously we don't have to attract funding. Our funding is internal. So I think at an academic institution, part of the tenure decision is can you attract external funding. So that's not a consideration here. Also teaching is not a consideration. So really it's focused on research. And I think the other thing that they I think put a premium on here more so than maybe an academic institution is the fact that we are privileged. There's no doubt I feel very privileged being here. Most of the time, I feel guilty [laugh] in terms of—

ZIERLER: How good you've got it, basically.

NEUMAN: How good I've got it. Yeah, exactly. But the flip side is that I feel an enormous amount of pressure.

ZIERLER: Not just how good you personally, but how good your research has it, too.

NEUMAN: Yes, exactly. But by the same token, I feel an enormous amount of pressure, because I'm given this opportunity and I have no excuse not to succeed. But by the same token, it's all on me. And I feel like the bar is slightly higher in terms of—they sort of say, "Look, you have nothing constraining you. You have to do well. You have to be—have to make an impact." And I think they also say, "Look, you have fewer constraints than a lot of your colleagues in academia, so we want you to participate more in the community." So they want more outreach. So editorship and that sort of thing, where you're actually—so I feel like that's part of this consideration.

ZIERLER: Would that include like membership to APS and Optics Society and things like that?

NEUMAN: Yeah, it's membership, but also more the membership on either leadership positions or—

ZIERLER: Active membership.

NEUMAN: Active membership. Yeah, exactly. That's right, that's right. Or a common one is an editorial board member, so I sit on the editorial board of the *Biophysical Journal*. So that's a contribution back to the community. So I think but past that, at the end of the day, I think the focus is really your peers. And that was made very clear to me, that they expect a certain level of research, and what really matters is do your peers think highly of you. And I think maybe the only other difference is again, because we're given so much and we're unconstrained in many respects, I think they dig a little deeper. So for example, it's a trivial thing sometimes, but I think they want 15 or 16 letters, for example. I think a typical academic position, it may be eight to ten. So it's not quite double but—so they really want a broad consensus in the field that yes, you're making an impact, that you're doing good work. But I think past that, it's a similar process.

ZIERLER: And when you got tenure, did it affect your day-to-day, or it was more like it was a monkey off your back?

NEUMAN: In the moment, I thought it was a monkey off my back, and I really felt like nothing changes, right? Or I just sort of—

ZIERLER: From a confidence level, was the affirmation—did you need the tenure process to know that it was there, or that was sort of more symbolic of what you had already known?

NEUMAN: At that point, it was basically if I get tenure, I get to keep doing what I'm doing, and if I don't get tenure, then I really—like everything changes. So it was not really a confidence thing, I think. It was more so just like could I cross that threshold, and could I keep doing it? I really want to just keep doing what I'm doing. But I think tenure is a tricky thing, and I think psychologically it really can be tricky to navigate. Because as soon as you get on this path—so let's say I'm an undergraduate, and I'm thinking, like, "OK, I'd like to be a professor," then that road—the eye of the needle is tenure. So whenever you make that decision—"OK, I want to be a professor"—that's ahead of you is this decision. So maybe it was as an undergrad, I already realized this. And what happens is you work—I tried not to focus on it, but you do, right? And you work so hard, and this is the goal, this is the goal, this is the goal. And you get there and you're successful. And it's a little bit, uh, disorienting. Because now what? What am I striving for? And actually I struggled, actually, with like getting my bearings after that. Because it was so focused on this one event. And to the extent I tried not to, but I couldn't—I can't help it. And then so past tenure was actually kind of a—

ZIERLER: It wasn't just liberating, is what you're saying.

NEUMAN: No. It was liberating, but too much freedom. All of a sudden, now, what's the goal?

ZIERLER: Now that you can truly do whatever you want, what do you do?

NEUMAN: What do we do? Exactly.

ZIERLER: But you're still probably—this metaphor of being a hub where other people come to you, that's still happening. You can always rely on that.

NEUMAN: Absolutely. Yes. But just sort of intellectually and psychologically, it was a struggle to sort of figure out, OK, what do I really want to do? And yes, the hub is nice, and I like the collaborations and whatnot, but I think also through tenure, you say to yourself, "OK, I want to take on maybe a bigger—" Up until tenure, you're just accumulating papers, and you're doing things. And after that, you sort of say to yourself, "OK, is there something bigger? Is there a bigger purpose I can take on or a bigger challenge I can take on now?"

ZIERLER: So how did you answer those questions?

NEUMAN: I'm still answering them. Tenure was only five years ago. So we were fortunate—with tenure comes new space, so we moved into a new lab. And so of course we're getting—I feel like all the pieces are getting into place. And so I feel like I'm just now I think coming back into, what are the big questions I want to address.

ZIERLER: Yeah. So this is the portion of the interview when I like to start to ask the big questions. So here it would be very appropriate to ask, what are the things—I mean, you're still a young guy in scientist terms.

NEUMAN: That's right, that's right.

ZIERLER: You have, god willing, decades of research ahead of you.

NEUMAN: Yep, yep.

ZIERLER: So what are the things that are exciting you, not like next week and next month, but in ten years, in 20 years? What are the big things that are really motivating you to answer this pressure you feel because of how good you've got it, and how you give back to that?

NEUMAN: Yep, yep, yep. Honestly, it's still a work in process, I would say. I think an overarching goal of mine is to really understand—we're coming at this from lots of different directions, I would say, now, in the field, but this notion of genome architecture. How is a genome sort of packaged? And we're looking at that from sort of a coarse grain measurement of like how big—big sort of scales, how are things connected up. And I think my contribution to that, I'm hoping, over time, will be understanding this role of how does the so-called DNA topology—so a lot of these models sort of skip the fact that DNA is actually wound up, and it's both overwound and underwound. And I feel like that has important implications in multiple levels. And so one, sort of at a gross scale, the genome architecture. And it's sort of a fascinating question of this is—if you take a ball of thread and put it in your pocket and take it out, it's a tangled mess. And yet our genomes are meters of DNA compressed in these tiny spaces, and yet we somehow achieve—manage to minimize these topological entanglements. And so that's a question of how do we go about that. And I think there's interesting models, but it sort of I think behooves us to really probe those models in detail.

ZIERLER: Because in the current state of play, these things are fundamentally mysterious.

NEUMAN: Yeah, there's a fundamental mystery. And there's some models, but I think we've sort of made a career [laugh] out of taking some very elegant models, and showing they're wrong.

ZIERLER: [laugh]

NEUMAN: And so they have to be tested, right? That's the purpose of models. And that's their purpose, and they serve a purpose.

ZIERLER: But you need models that can be proved *right*.

NEUMAN: Yes, exactly.

ZIERLER: For it to be clinically valuable, I suppose.

NEUMAN: That's right. Or to just understand. And so I feel like at multiple scales, I feel like the sort of fundamental process of how the DNA is overwound and underwound plays out on multiple scales. So on a gross scale, it changes how the DNA is organized. And conversely, the organization of the DNA has to take place in such a way that you don't create sort of topological problems. And so understanding that process, so that cross-section of genome architecture and topology is one sort of big question. And then this also boils down, though, because at the opposite scale, you have enzymes that are acting on DNA. You have the polymerase that I worked on as a graduate student, has to get entry to the DNA. And it turns out that that whole process is tightly coupled to—so when the polymerase moves along, as I mentioned, it's a rotary motor, but if you take a rotary motor, and you think about it sort of spinning along some sort of shaft, that's fine. But now, if you say, "Well, that motor is now fixed"—and so now, instead of the motor moving along the shaft, the shaft is spinning, but now that shaft that's spinning is actually these two intertwined strands of DNA, you end up with all sorts of what we call topological problems. The DNA is overwound ahead of the machinery but is underwound behind it, and all of these things have to be regulated and taken out by these enzymes that we study. So again, this sort of coupling between how the DNA is—the mechanics of the DNA and how it's overwound and underwound, how that impacts the enzyme processes that are both—directed processes—this transcription or replication—and also more subtly and more generally how does the effect of the so-called DNA topology, how does it affect all kinds of different enzymes that are interacting with the DNA? My supposition is that there will be classes of enzymes that are strongly coupled to this, and classes of enzymes that are more weakly coupled. And so a for instance in this case is—again, as I mentioned, DNA damage is prevalent and very toxic. And so we have a whole machinery dedicated to basically searching the DNA for DNA damage. But an open question—and so one classic problem in DNA is if I'm replicating DNA, and I start with a parental strand—my ACGT—and I should faithfully duplicate the complement every step along the way. So every A should get a T, and every G should get a C and then vice versa. And if I make a mistake, a so-called mismatch—and that happens, right? With some low but finite probability, I have a mismatch. And so now all of a sudden I've created a DNA that has a mismatch, and you need to find that somehow. So if the polymerase goes on, it leaves it behind, doesn't care, it's done. But now you've got this mismatch in the DNA, and there's a whole host or a whole battery of biological machinery to find that. But a realization is that you could use this sort of underwinding or overwinding of the DNA. So if I take a hose, a long piece of hose, an infinitely long piece of hose even, and if I put a kink in it, then when I twist that up, the hose will buckle and form that plectoneme structure right at that kink. And so this is an hypothesis we've had and we're following this up—the same thing happens to a piece of DNA. So if it's damaged, if there's a defect site, if there's a mismatch, and I twist up that piece of DNA, then it will actually buckle and form a plectoneme right at that site. And so this is—we're in the process—so we've done the mechanics now. We've done the sort of fundamental physics to show this is the case. We understand how this works from a fundamental standpoint from both now experiment and more recently theory and simulation. And now what we're testing is the ansatz [?] is that these enzymes will actually specifically look for the structure—and in fact this is my work of my colleague Wei Yang is showing this—indeed, what these enzymes are looking for is exactly the structure that gets presented by this sort of buckled DNA. And so our novel hypothesis is that the topology of DNA is helping find all these defect sites, all these damage sites in the cell. And this has been a missing connection. If I have four billion bases and I have one mismatch, you can't scan four billion bases in a lifetime. How do you find that? And this has been a missing sort of subtle question: with a finite number of enzymes, how do you find these places?

ZIERLER: Does machine learning play a role in this? Computational power?

NEUMAN: Machine learning helps us on the back end, but in a cell, there's no machine learning. And so what we're claiming in the cell is that it's this sort of mechanical process of winding the DNA. These buckles now, sort of very physical mechanical process, presents the DNA in a particular way, and now the enzymes can find it very easily. So that's a for instance, but I think there's many instances of this. And so understanding in a global sense how does this topology of the DNA impact the life of the cell, how it repairs DNA, how everything works, has been something that has been I think underappreciated in biology to an extent. And that's I think my big push, if you will. That's one aspect. And coming back to physics, another thing that actually really got me started, and I'm still pushing on this, is this notion that in biology—physicists tend to be reductionist, so we take our little motor protein, we take our little, our topoisomerase or other enzyme that manipulate DNA, we look at them in isolation. We say, "Aha, we measured something. We can figure out how this works." Which is true. But, what we discover from biology is that none of these enzymes work alone. They always work in sort of large complexes. And this is something I've taken on as sort of a challenge, an intellectual challenge, is can we move from the sort of isolated enzymes up to these full complexes that are working in vivo. And from a physics standpoint, we talk about emergent behavior. So sort of an intellectual challenge that we're following up on, on several different fronts, is how do you go from the activity of an individual to this activity of a group. And can you understand that sort of—is the whole simply the sum of the parts? Are you just putting everything together at the same place at the same time, and they just do their thing, and they're just—there's some—just by having everything working together, that's how you end up with a product that works? Or, is there something more interesting? Is there some sort of communication? Are you getting some sort of synergistic activity? And one of the systems we've been working on is exactly that, where you take enzymes that do very different things, you couple them together, and together, they can do something that neither one alone can do. And so understanding that process and sort of building that process up in an intellectual standpoint from the single molecule approach, building from the individual components, understanding in detail what they do, and then how do they combine to give us this extra activity. And that's another sort of I think a big intellectual challenge that we're trying to figure out.

ZIERLER: So bringing this physics perspective into biology, is there a unified theory of biology that you are contributing to? Or is that like way too expansive for you? I mean because clearly, there's something for you to unlock.

NEUMAN: Yes.

ZIERLER: But the question is, is your vista of what there is to unlock, is that part of the larger question that needs to be unlocked, or is it sort of a self-contained category of knowledge?

NEUMAN: I think this is a real—this question crops up a lot at the interface between biology and physics. Physicists tend to be—we tend to be reductionists and also maximalists. So we like to look at very simple things—

ZIERLER: Right. [laugh]

NEUMAN: —and we like the maximal theory of everything, right? And I think biology really rails against that in some sense, because I feel like in biology—the biologists will tell you that details matter, and that this system is identical to this system but different, and those differences matter. And so I feel like biology is—but there are some overarching principles, and so I feel like we're trying to do both. We're working on a system, which is closed. So yes, it's a very particular system. And so the biologist in me says, "Yes, we're going to understand how this system works." And this has important ramifications for cancer, for genome architecture, for genome stability, for aging. So it has its own—understanding this in detail has its own set of important ramifications from a biological standpoint that are still limited. But my hope is that—again, as a physicist, you don't have to work on every particle. You work on a particle that tells you something about every particle. And so the question is, are there principles of how these things operate and how they act together that we can abstract from these closed systems?

ZIERLER: Right.

NEUMAN: And so this sense of—I think maybe the DNA topology is a cleaner system, right? A few enzymes—if we study what are the detailed interactions of how they're interacting with these different structures and how do they represent that and how do they probe it and how does it impact them, then we can build up some general knowledge and some general considerations. So again, this role of—it's an ongoing project, but I think it highlights the sort of notion that all of a sudden, you can take a defect in DNA, and you can now discover that sort of non-locally by applying this—by twisting the DNA. So I think that could be—we're focused on a very particular aspect of that right now. That would be very general. And the question is, how general is that? And that's yet to be determined. But that's a more general sort of thing, that you've introduced a new fundamental approach to how the DNA can be sort of processed, or how you can differentiate different parts of the DNA through this coupling to this physical property. Which is very general. So I can say that's more general, more overarching. Or these big questions of topology and organization—how do you keep from being knotted? That's a statistical physics problem. That's a biological problem on a big scale. But invariably what we ended up finding is different—evolution is a tricky thing [laugh] and I feel like what we end up seeing in biology is that the same problem is solved in different ways. And so yes, we can propose a universal sort of problem or universal structure, but biology has solved it in different ways, and so we can't say there's a universal—it's an organic thing. And so I think that's where this tension comes from. As a physicist, I can say, "Oh, we have this problem of entanglement of DNA, and how is that solved?" And I can be a physicist and a statistical physicist and I can write down some nice equations, and I can write down some nice properties, and say, "OK, it must be like this or like this." And then when you turn to biology and the answer is, "Yeah, there's this, this, this, and the other." And there's three different ways this is solved, or five different ways this is solved in different ways in different organisms and different approaches, and they can be distinct. And so I think that's where this—it's a messy interface between physics and biology.

ZIERLER: So when you're talking about the ramifications for things like cancer and aging and heart disease and things like that, what's your feedback mechanism to know if you're moving the needle in these regards?

NEUMAN: So I think this has been a real evolution for me, I think. As a physicist, you start out and you think—you're measuring a machine, right? And if I can measure the machine, I can measure the properties of this machine, I'm really excited, right? I've learned something. And what I've learned over time is that you really have to speak to the—you have to connect these intimate details that you're finding out to a broader picture. And so I feel like if I can make that connection, and I can somehow take a problem that has been posed in the biological field—not in the biophysics field—but if my biophysical measurements are somehow impacting the broader biological field—if I can say, "Here's a problem that you've faced and you had not been able to address or can't explain, and my biophysical data now provide an explanation for this broader biological question"—that's sort of my feedback. And so it's not—

ZIERLER: You don't see—there's not a Jonas Salk moment with your research?

NEUMAN: No.

ZIERLER: That's not how this works.

NEUMAN: Yeah, we're not—we're several steps removed, I would say. Occasionally we bump into real biomedical problems. But I'd say we're a few steps removed. But again, being here is interesting. I have colleagues who are cardiac—I'm in the Heart, Lung and Blood Institute. I have cardiologist colleagues. And so we worked on collagen for a while, and we had this interesting finding that collagen, through an elegant physics principle, actually, it stores—there's internal strain in collagen. And so similar to like I would say mud cracking—because mud dries as it cracks—collagen goes through the same process. In fact, it sort of spontaneously cracks open. And this is how enzymes that process collagen actually get entryway into the collagen. And what happens is when you put strain on this, then it heals and it prevents it from being damaged, and prevents it from being processed. So I present this work to my colleagues, and my cardiologist colleague takes me aside afterwards. He says, "You know, this is very interesting. We have fibrotic heart patients." And so they come and they have fibrosis of the heart. He said, "It's a lethal condition." But one temporary cure is they actually stop the heart for a period of time, they put them on a heart machine, the heart is stopped. So the tension on the heart now goes to zero, essentially, and effectively zero. And he says, "After several days, when we restart the heart, we see improvement." And now this is a weak connection, but he said, "This is something I want you to think about." And maybe we'll get back to this, but this connection between sort of the stress on this collagen that we're showing is important for how it's processed, and the fact that in a fibrotic heart, if you can stop it, then it seems like the fibrosis is remedied to some extent. So there's a long connection there, but that's the sort of thing that I feel like I'm exposed to here. Making that connection? I'm not sure, explicitly. But at least it gives us something to shoot for. And it gives us a broader context. And I think the work we're doing is at least one or two steps removed from really frontline biomedical research, right? I'm not—we're not going to cure anything, at least not explicitly. The photodamage results aside—

ZIERLER: You yourself, but you could be part of something larger that cures something.

NEUMAN: Right. And the way I see it is that this research—some of it will contribute. And I think some of the research we're doing, particularly on these topoisomerases, are important targets for both chemotherapeutic and antibacterial—particularly antibacterial work. And the extent that—I guess I work on the promise that there's a likelihood that by understanding really fundamental processes of how these enzymes work and how they can be inhibited or poisoned by these drugs will give us insights in how to make better drugs, or how to make different classes of drugs or at least to focus our efforts on, what are we actually looking for? And so that's part of our research is focused on that aspect. But will we discover that new drug? No. Will we help somebody test their new drug? Yes. And again, coming at this as a physicist, it's not really—that's part of it, but I think the bigger part of it would be, can we establish guidelines? What's the bigger picture? And again, this is why the work was really compelling for me, was sort of taking clinically relevant data on one axis and single molecule physics data on the other, and showing this perfect correlation, and making a correlation that had never been made before. And so we can tell them, "We know why you're killing your cells, and this one particular aspect of the interaction between your poisons and this enzyme—we know what that is. And if you want to optimize this in the future, you optimize on this. I don't care about the other stuff it does. There's all kinds of different effects it has on the enzyme. But there's one effect that matters, at least in terms of how they're killing cells." So that's the kind of thing we can do. But in terms of day to day, we're still biophysicists. We're still—"How do things work?" And I would say that's—we're really about mechanistic kind of questions, and sometimes those bump into—but I think just being in an environment like NIH, my colleagues are clinicians, and I talk to them, and there's feedback from them in a general sense. And the things I work on, they give me broader context. Again, in work that I sort of spun off to a postdoc who left the lab, and now she's starting her own lab, but in terms of human health—so another class of enzymes we work on are helicases. These are enzymes that move along DNA and they separate the DNA strands. And these are very important in DNA repair, because basically you can sort of imagine—if you're fixing a train line or something, the first thing you do is you pull up the track [laugh] and you put down new track. And so these helicases are responsible for the pulling up off the track, the separating of the track. And there's really horrific human diseases that are associated with these enzymes.

ZIERLER: For example?

NEUMAN: Werner syndrome. Or Rothmund-Thomson syndrome. So these are very rare autosomal diseases that lead to—so it's progeria is early-onset aging. So Werner syndrome is an aging syndrome in some sense. But also chromosomal abnormalities, and then a high preponderance of cancer. So these patients are getting all kinds of very specific cancers, and it has to do with the fact that they're missing repair pathways. And so if you can't repair it, then it generates a cancer. Very specific skin cancer, for example, very common. Also developmental delays. They're really horrible diseases. But people live. And so we have a colleague here who studies a particular—it's XP Xeroderma pigmentosum —blanking on the name. But it's a known condition. It's a genetic condition. It tends to be defects in repair, so it leads to cancer, other developmental delays. And what he has is - NIH is sort of one of the few places in the world where we take on these rare, rare diseases. So some of these diseases, maybe there's only a few hundred patients in the world, maybe. But he has catalogued 30 or 40 patients and he has their DNA. They have different—so clinically, they have different manifestations of this disease. They've all mapped it back to the same enzyme, so they know there's some defect, but they have different clinical manifestations in terms of how they actually present. What are their clinical sort of manifestations of this? And with the postdoc who just left the lab, I've sort of put them together—they can now make each one of these enzymes and study it at the single molecule level and understand in detail what are the molecular changes that are taking place that lead to different—right? And so is that a cure? Maybe not. But is it contributing to like a fundamental understanding of what are these enzymes doing and possibly ways to mitigate this? If we can find—there's a commonality, and missing this component, can we either fix that, or can we add something else to address this particular aspect of this important thing it's doing, and maybe miss some of these other aspects? So do I feel like are we on a cure? No. Are we helping really understand at a deep level how things work? Yes. And being at the NIH was really eye-opening to me, because I really expected to come here and do my thing. And I expected to collaborate with people, but again very much on the basic side of things. And it has really been I think very compelling and eye-opening for me to just have colleagues who are clinicians, and occasionally we overlap, and there's a connection that we can do something together.

ZIERLER: Two final questions. One, philosophically, are there things that remain as mysterious to you and to your field from when you started as they are today? And projecting forward, would you be able to reasonably extrapolate that they will indefinitely remain mysterious, and then that assumption might in turn color your appetite on whether or not to pursue that particular line of inquiry? Or is it really wide open and you're open to basically—if it exists, it might be knowable to understand how it exists.

NEUMAN: Addressing the second half of that first, I think—I'm wildly optimistic. I think given the right set of tools—and sometimes it's—and so I feel like that's my perspective, because a lot of what we do is build tools. And the way I see it is that if I see a problem, and there's a hypothesis of how it might work or a way of testing it and what is required is a tool, then that's where we really shine. And that's where we bring something unique to a place like the NIH. You can't buy it off the shelf, but if there's some way of teasing out that problem that we can do with a tool, then I feel like that's our ability. And so I feel like the question sometimes is just, "Do we have the right tools?" And I think that's in my mind—coming here as an experimentalist, I really feel like that's the question. Can we ask the right question, and do we have the right tools to address it? And I think sometimes we don't have the right questions yet. We know there are certainly problems I think we don't understand.

ZIERLER: And obviously you're talking about the hows, not the whys.

NEUMAN: Yeah, I mean the whys are—it is what it is. I think there's questions about—again, I come back to—my bread and butter is DNA. It's important in lots of ways. I think we're still understanding how this overall architecture works, how it's imposed. And I think there are some questions that are difficult because it's such a massive scale. And we tend to work on very small-scale things, and this is a much bigger scale. So that has been a challenge, and I think addressing that is a challenge for us. But it's a healthy challenge. It's something that I think is interesting. We will take new tools, new approaches, but I view that sort of scaling up what we've been working on to a larger scale, and understanding at the level of millions of bases, how are things organized? And I think we're understanding some principles from cells, but can we recapitulate that in an in vitro environment and can we really learn fundamental mechanistic things? Can we rebuild that? And so we're seeing organization take place in a cell, and we're probing that, but I think an open question for me is back to Feynman, right?—"What I do not control I do not understand." Can we recapitulate this in an isolated system? And then we really understand it. I think that would be an exciting place to go.

ZIERLER: OK. And then last one—

[break]

ZIERLER: A remarkable theme throughout our discussion has been this interplay between your education and how you've applied it. You're clearly such a good student in terms of your learning. You don't have to say that; I'm going to say it, just based on the way that you've characterized your professional and intellectual trajectory. So my question is, you've learned a lot, but what are the fundamental concepts in physics that you return to, day in and day out?

NEUMAN: So the fundamental physics I think that I return to is somewhat ironic since it was a poor subject of mine when I learned it, was statistical physics.

ZIERLER: Statistical physics.

NEUMAN: Yep. So biology is living in a thermodynamic world, right? We're governed by statistical physics, and so that's really—

ZIERLER: So can you explain that? Why are we governed by statistical physics in a thermodynamic world? What do you mean by that?

NEUMAN: Well, because we're living—everything is driven by entropy. And so we're living in this entropic bath, right? It's all fluctuations. And fluctuations dominate biology. Everything that happens is stochastic. Everything is statistical. Nothing happens like clockwork. It sort of happens like clockwork, but that's hard to do in biology. Most things that happen in biology are really an assembly—at the fundamental scale, it's all stochastic processes. And so it's all noisy, stochastic processes. And the magic, in some sense, is that you can—out of this disorder emerges life and order. But fundamentally all these processes are really governed by statistical physics. It's really governed my thermal fluctuations, by entropy, by noise. And at the level at which we worked, this is what we were confronted with consistently. Everything we look at is really governed by sort of statistical fluctuation, by noise, and we're extracting signals out of that, but also the enzymes themselves are working, they're working in a thermal bath. Everything is in this messy thermal bath. So I think that's the sort of scale at which we work. And none of it is deterministic. We're not at the level of quantum mechanics. I think there are some biological systems that work at quantum mechanical levels, but I think we're really at more of this sort of messy statistical physics. It's an ensemble. It's a soft ensemble of things. And it's really relying upon—like the energies are all on the scale of sort of kT. And so we're right at the thermal energy scale, and that's where everything is happening, and it's really just a matter of introducting a little bit of energy, but fundamentally it's all governed by thermal processes, which sort of come back to statistical mechanics. It's sort of ironic that I ended up studying this, since I have to say, of all my subjects, that was probably my weakest. But I have a habit of like somehow like [laugh] ending up in those places.

ZIERLER: You could say that's cosmic comedy or something like that.

NEUMAN: Yeah, it really is. I laughed and laughed—my postdoc was in the laboratory of statistical physics, and I just was thinking back to Marv Cohen at Berkeley just shaking his head, like "I can't believe this." [laugh] And so yeah, I would say that's—on a day to day basis, I think that is—when it comes to biology, it's really the statistical physics is really what's important, I think in terms of governing the scale at which we're working. So we're working at sort of individual enzymes, individual proteins, the mechanics of polymers. So I would say if you think about polymer physics, it's sort of a subset of statistical physics, that's sort of the interface. We're looking at—proteins can be treated as a certain kind of polymer. Obviously, DNA is a polymer. And because everything is at this sort of energy scale of kT—and some of the systems we study are really—it's interesting how biology has harnessed thermal fluctuations, right? And we have these Brownian ratchet systems, right, that obviously consume energy. We know enough physics to avoid the fallacies associated with thermodynamic laws, but they can harness thermal fluctuations with a certain amount of energy to do work in interesting and useful ways. And so I think that's the scale. That's really—I would say that's the day-to-day bread and butter. And then in terms of building, I really think it's optics and understanding optics. So back to Jackson. [laugh]

ZIERLER: Yeah, back to Jackson.

NEUMAN: Back to Jackson. That's right. And so I would say those are the two on a day-to-day basis that really—those are the aspects of physics that really—but I would say more importantly, what's fundamentally different is just the approach. It's quantitative. It's sort of a systematic approach. It's governed by—you feel like it should be governed by laws. And so I think that I would say more important is the sort of mindset or that approach to science that you end up with. Just trying to understand bigger principles. Trying to make sure that things make sense and sort of are self-consistent. And I think there's a great deal of power—also this sense of modeling. And ideally—it's hard, and you may not always be successful, but this notion that if I really think I've succeeded, I would like to be able to write down a model, and something that's quantitative, and predictive. And I think those kind of senses come from physics. And I have a great deal of faith, still, in theoretical physics, and sort of even applied to biology. And so I think that's what we're pushing towards. I would like to be able to make these measurements such that either myself or someone else can sit down and take these measurements and understand, and now write out some series of equations or some series of models that are very, very physical, and explain the biological process at hand.

ZIERLER: And that these avenues of inquiry can exist long after your retirement, right?

NEUMAN: Absolutely. Absolutely. And I think this question of what can we address, I think it's a matter of scale, and it's a matter of, what level can we think. I view this as like a ping-pong game where the experimentalists make measurements, and that pushes—the foundation of the theories are promoted and then tested and discarded or extended, and then that pushes back into the theory camp. And now with new data, you can think at a new scale, and back and forth. So I think it's just a matter of—you need this sort of tension between the two, and that they push each other forwards. And so the things that we can't even conceive of now I think are just a matter of building up the right level of experience. And that's why I think the fundamental sciences are so important, because this is—you build it brick by brick. And is our research really important for biomedical research today? Maybe not. In 20 years, maybe three or four little elements that we found could be crucially important for someone's theory or someone's approach in 20 years.

ZIERLER: And that, in and of itself, is what gets you out of bed every day.

NEUMAN: Yeah, yeah. And just understanding how the world works. It's amazing as a physicist to look at the beauty and the complexity of nature, and these incredible machines that are on these molecular scales, and the work that's done, and the physics that's done. You know, converting or—not converting, but harnessing thermal energy in smart ways to drive directed transport is really—you know, these are beautiful physical machines. And sort of teasing that apart is really fun.

ZIERLER: Well, Keir, this has been an absolute delight. Thank you so much for spending the time with me.

NEUMAN: Oh, sure.

ZIERLER: This is going to be a tremendous resource for lots of people coming from lots of disciplines. So I really appreciate it.

NEUMAN: It was fun.

ZIERLER: Thank you so much.

NEUMAN: Absolutely.

[End]